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OBSERVATIONS ON HUMAN FOLLICULAR AND TUBAL OVA

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STUDIES concerning the maturation, fertilization, and early development of the female germ cell have been made in several mammals, both in vitro and in vivo. After exposure to spermatozoa in vitro, cleavage has been reported in rabbit ovarian,[1, 2, 3] tubal,[4, 5, 6] and uterine ova,[7] as well as in guinea pig[1] and human [8, 9, 10] ovarian ova. Two human eggs, of the two-cell and three-cell stages, have been obtained from follicular ova exposed to spermatozoa and placed in human blood serum.[10] In the rabbit,[11] guinea pig,[12], rat,[13] mouse,[14] and monkey[15] tubal ova fertilized in vivo have been found to undergo cleavage.

The formation of a second polar body has been noted in insemination experiments on rat eggs in vitro.[16, 17] The first polar body has been seen in human follicular germ cells after they had been kept in blood serum or follicular fluid from 3 to 24 hours.[18, 39] It has been shown that in the human being, as in almost all mammals, the first polar body is given off before ovulation.[19, 20, 21, 22] The conclusion has been drawn that, when rat follicular ova, matured to the earliest phase of miosis, are transferred to the ovarian bursae of mated animals, fertilization occurs with normal offspring resulting.[23]

Spermatozoa have been observed in the zona pellucida and what were considered to be male and female pronuclei in the cytoplasm of human eggs removed from Fallopian tubes after coitus had taken place.[24, 25] Penetration in vitro of spermatozoa through the zona pellucida and of a single fertilizing spermatozoon into the cytoplasm of the rat ovum has been reported.[26] Also, it has been stated that the entire fertilizing spermatozoon may enter the cytoplasm of the mouse,[27, 28] rat,[17, 29, 30, 37] guinea pig,[31] rabbit,[4, 32] and bat[28] egg.

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An ovum that had divided into two spherical cells and which also contained two polar bodies and an intact zona pellucida has been recovered from the middle third of the human Fallopian tube.[33] Studies in the monkey,[15] mouse,[14] and human being[9] indicate that fertilization usually occurs within 12 hours after coitus.

In so far as can be ascertained, all of this work has been carried out by means of the conventional histologic and/or microscopic methods. Employing phase contrast microscopy, excellent photomicrographs have been published showing the cytology of living rat eggs immediately upon their removal from the Fallopian tube.[34-38] Of special interest are those showing that, with the exception of the end-piece, the entire fertilizing spermatozoon enters the cytoplasm of the ovum. The phase contrast microscope is markedly superior to the standard one for observing and photographing the cytologic detail of the living cell. Fixation produces marked changes, e.g., shrinkage of the zona pellucida, precipitation of the contents in the perivitelline space, as well as alterations in the cytoplasm and nucleus. Upon sectioning there is also the possibility that a spermatozoon may be displaced into the cell artificially. Accordingly, the present observations have been made by means of phase contrast microscopy, in an attempt to gain a more accurate and complete cytological understanding of living human follicular and tubal ova, before and after their exposure to spermatozoa in vitro.

Materials and Methods

Follicular ova were obtained from ovaries prior to or immediately after their removal from patients undergoing gynecological surgery. The follicles, grossly normal in appearance, ranged in size from 3 to 16 mm. in diameter. Aspiration of the follicles was accomplished with a sterile syringe and a 22 gauge needle. The needle was inserted into the ovarian tissue 3 to 4 mm. away from the edge of the follicle and then passed into its antrum so as to enter through the base, hence obviating any leakage of the follicular fluid. All normal-appearing follicles were likewise aspirated in succession with the same syringe and needle, thus pooling the ova from a given ovary. The fluid was then taken immediately to the laboratory, expressed into a sterile Petri dish containing a petrolatum ring 3 to 4 cm. in diameter. Sterile physiological salt solution, placed outside the petrolatum ring, served to prevent evaporation of the follicular fluid.

After ova had been identified, they were photographed in phase contrast. Then either a drop of fresh normal semen or semen and small pieces of homologous tubal mucosa were added either to the entire amount of the follicular fluid or to one-half of it, the other half of the fluid and contained ova serving as a control. All preparations were observed microscopically, then covered and incubated at 37° C. After 3 to 24 hours of incubation, they were removed from the incubator to room temperature and the ova transferred individually with a very fine pipette into a small drop of the follicular fluid on a glass slide. A petrolatum ring was made around the drop and a cover glass placed so that it touched the fluid but without direct pressure upon the ovum. In order to have a petrolatum ring of uniform thickness, the petrolatum was expressed from a syringe through an 18 gauge needle without bevel. The ova were then studied with the Spencer phase contrast microscope, with magnification of 100, 200, 430, and 970 times.

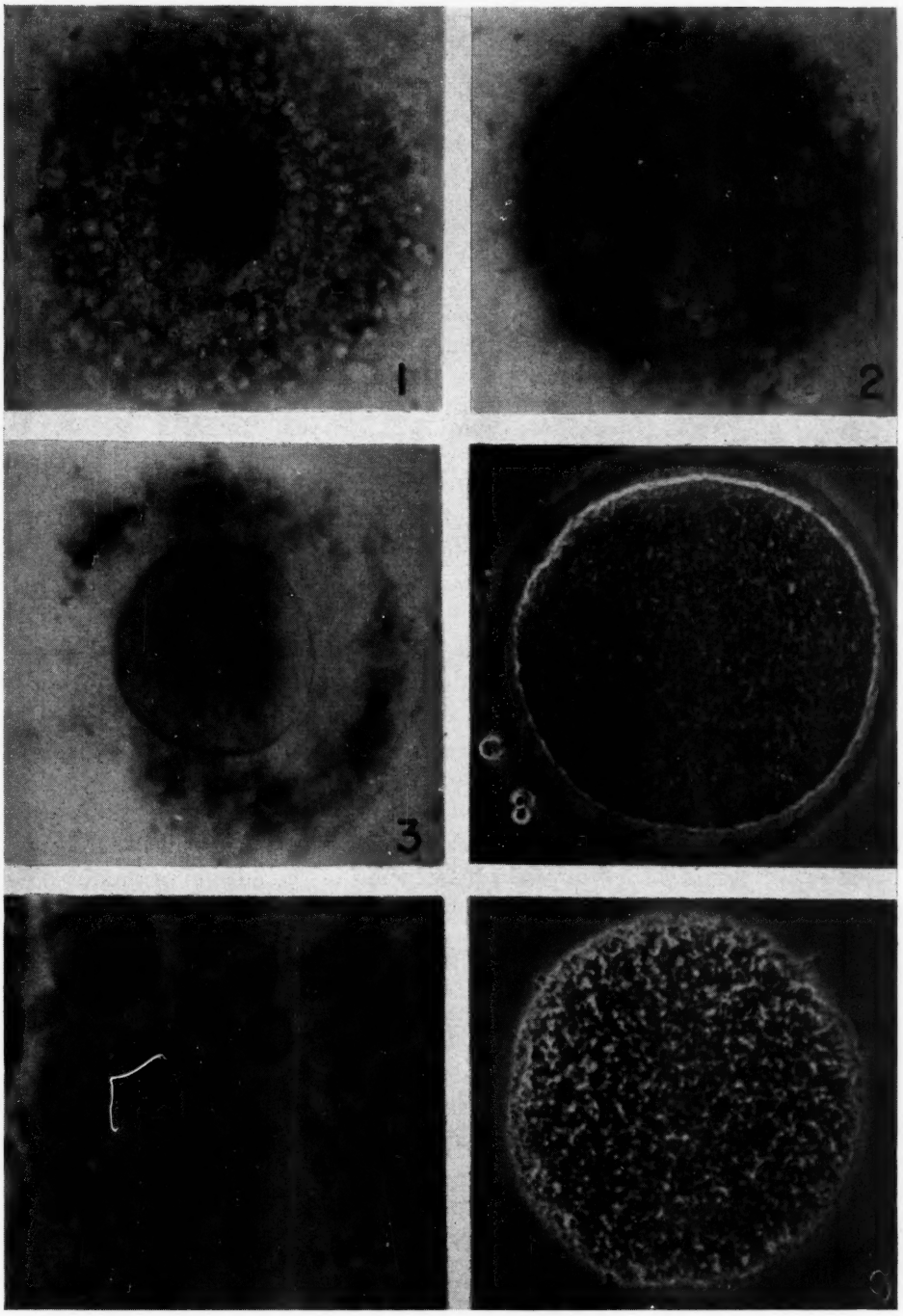

Fig. 1.—Follicular ovum before exposure to spermatozoa. (×100.)
Fig. 2.—Follicular ovum after exposure to spermatozoa. (×100.)
Fig. 3.—Follicular ovum showing partial denudation. (×100.)
Fig. 4.—Follicular ovum showing complete denudation. (×100.)
Fig. 5.—Globules in perivitelline space. (×970.)
Fig. 6.—Ovum in Fig. 4 without zona pellucida. (×100.)

The tubal ova were washed from normal Fallopian tubes immediately upon their removal from patients whose ovaries showed evidence of a recently ruptured Graafian follicle. The Fallopian tubes were irrigated with a 10 cm. sterile glass pipette 6 mm. in diameter and equipped with a rubber bulb. The pipette was filled with sterile homologous blood serum, the tip inserted into the distal part of the tube for a distance of 1 cm., around which a ligature was placed to prevent leakage. The ovum was then washed into a sterile Petri dish. After it was photographed in phase contrast, a drop of fresh normal semen and small pieces of homologous tubal mucosa were added to the serum. The behavior of the spermatozoa and the egg was observed, and then the preparation was covered and incubated at 37° C. After 3 to 24 hours of incubation, the ovum was prepared for phase contrast study in the blood serum.

All photomicrographs were taken on 35 mm. microfile film with a Leica Ipso camera.

Results

Follicular Ova.—Upon aspiration these ova were normally surrounded by the corona radiata around which were almost invariably some of the cumulus cells (Fig. 1). In almost every case, an ovum was obtained from a normal-appearing follicle and the follicular fluid was clear and straw colored. The largest number of ova obtained from one ovary was 16.

After a drop of fresh normal semen was added to the follicular fluid and the mixture kept at 37° C. for 24 hours, there was only partial dissolution of the corona and cumulus cells, i.e., denudation of the ovum was not complete (Fig. 3). On the other hand, when small pieces of homologous tubal mucosa were also added, denudation of the ovum was complete or nearly so by the end of 3 hours (Figs. 4, 9, 11, 15, 17, 18, 19). No disperson of the cumulus was observed in control ova after 24 hours of incubation at 37° C. Hyaluronidase, which was added to the follicular fluid instead of the semen and tubal mucosa in some experiments, failed to effect dissolution of the corona or cumulus cells. The corona and cumulus cells in the ova treated with hyaluronidase and in the controls after 24 hours of incubation remained firmly adherent to the zona pellucida upon agitation of the dish containing them. Aspiration and expression of these ova several times through a very fine pipette failed to show any evidence of dissolution of these cells. By the end of 3 hours the same treatment of the eggs in the presence of fresh normal semen and tubal mucosa, on the other hand, usually resulted in ova surrounded by only the zona pellucida. These observations are based on approximately 50 control and over 200 experimental eggs.

The diameter of the living ovum, to the outer surface of the zona pellucida, was more than 90 microns in the majority of the specimens, the largest egg measuring 135 microns.

Movement of the vitellus within the zona pellucida was often observed in the denuded normal ovum upon slight agitation. The larger ova were eccentric within the zona pellucida (Figs. 9, 11, 17, 18, 20). As a result, when the eggs were rolled about in the dish or on the slide, a definite polarity was demonstrated, i.e., they lay finally with the narrowest portion of the perivitelline space between the ovum and the surface of the container.

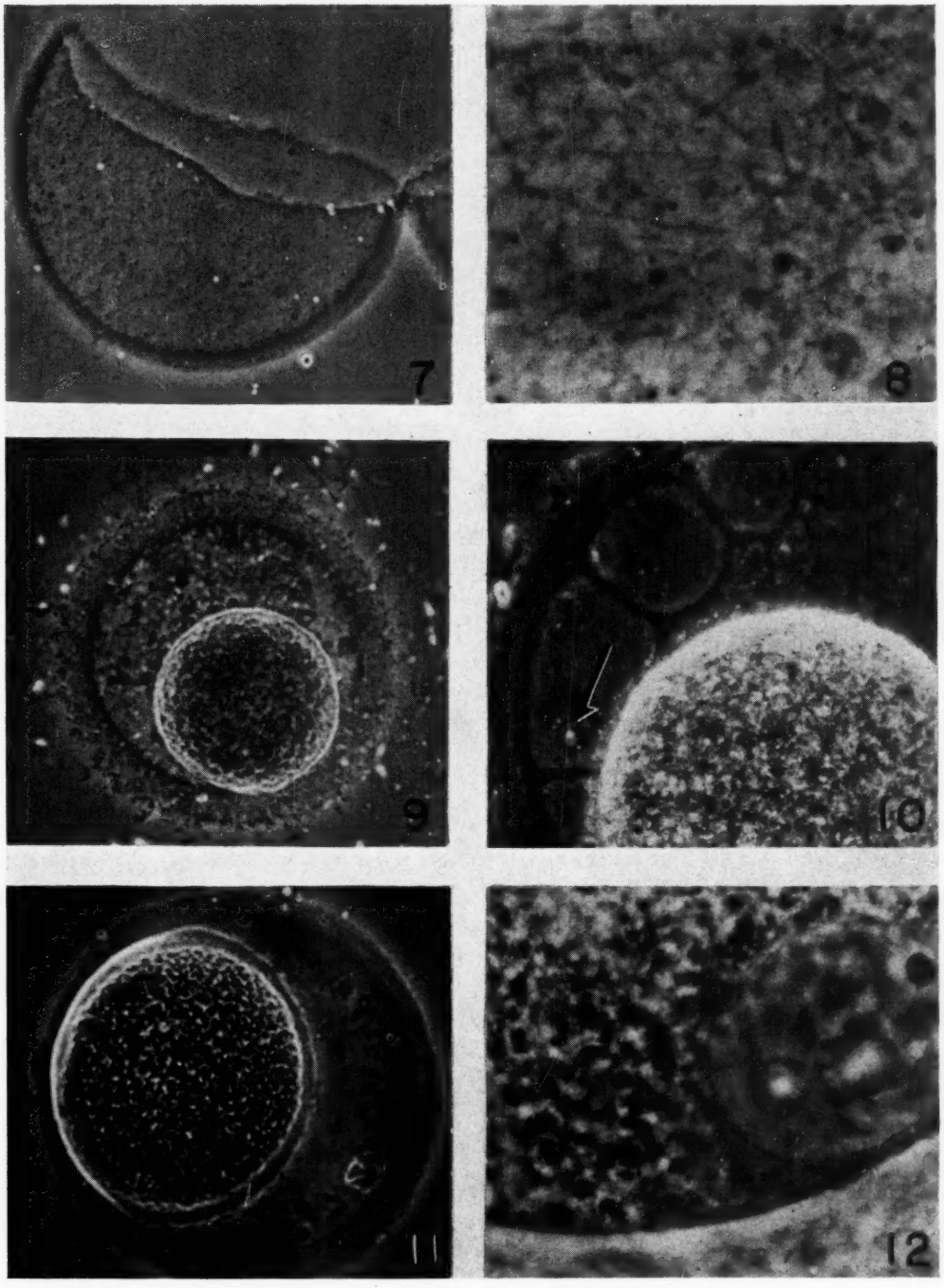

Fig. 7.—Zona pellucida from ovum in Fig. 4. (×100.)
Fig. 8.—Fibrils with granules in zona pellucida. (×970.)
Fig. 9.—Spermatozoan behavior about egg; globules in perivitelline space. (×100.)
Fig. 10.—Spermatozoon and globules in perivitelline space. (×200.)
Fig. 11.—Follicular ovum with vitelline membrane. (×100.)
Fig. 12.—Nucleus of follicular ovum undergoing first polar body formation. (×970.)

Soon after the semen was added to the follicular fluid, the spermatozoa surrounded the cumulus and corona cells (Fig. 2). After denudation the spermatozoa covered the surface of the zona pellucida almost completely (Fig. 30). In no case was there any evidence of trophic influence of the ovum on spermatozoa. Spermatozoa were observed swimming in the closest proximity to the egg and yet passed right by it without apparent attraction (Fig. 9). However, having once accidentally touched the ovum, the vast majority remained in contact with it. At no time was there any falling away of the spermatozoa from the zona pellucida or suggestion of a fertilization membrane forming. With hundreds of spermatozoan heads rotating against the zona pellucida at right angles or nearly so, tails moving vigorously, the ovum was very often rotated in the clockwise direction. The ovum was often moved about within the medium and simultaneously rotated. The maximum rate of rotation was measured at 360° in 15 seconds. This phenomenon was observed repeatedly while all other cellular particles within the medium remained stationary. Cinematographic records of the behavior of the spermatozoa about the egg were made. Spermatozoa were observed to rotate on their longitudinal axes while their heads were against the zona pellucida.

In Figs. 5, 9, 10, 19 can be seen globules within the perivitelline space. These globules were noted in many of the eggs. Without phase contrast they were not discernible, or very faintly so. They were homogeneous, translucent, and varied in size, having the appearance of fat globules. Granules of different size, shape, and density were also present in the perivitelline space (Figs. 5, 11).

The vitelline or cytoplasmic membrane of the ovum was normally represented by the limiting boundary of the cytoplasm or ooplasm (Fig. 6). The constituents of the ovarian cytoplasm were distributed evenly throughout (Fig. 6). Of all the ova examined, only one showed a distinct vitelline membrane (Fig. 11).

The zona pellucida was found invariably to contain interlacing fibrils (Fig. 8) on which were situated dark, fine granules. This network of fibrils extended through the entire thickness of the zona pellucida. Under oil immersion, pressure upon the cover glass resulted in a decrease in the interfibrillar areas and an attenuation of the fibrils. Release of the pressure showed that these changes were reversible. Under the lower objectives, pressure upon the cover glass resulted in an increase in the circumference and a decrease in the thickness of the zona pellucida. Release of the pressure showed that these changes were also reversible.

The ovum shown in Fig. 9 was completely denuded after three hours of incubation at 37° C. in follicular fluid to which fresh semen and tubal mucosa were added. The egg was then washed in physiological salt solution, after which it was placed in follicular fluid without spermatozoa. A small drop of semen was added at a distance from the ovum and as soon as the first spermatozoon came in contact with the zona pellucida the ovum and the spermatozoon were gently transferred into another drop of the follicular fluid

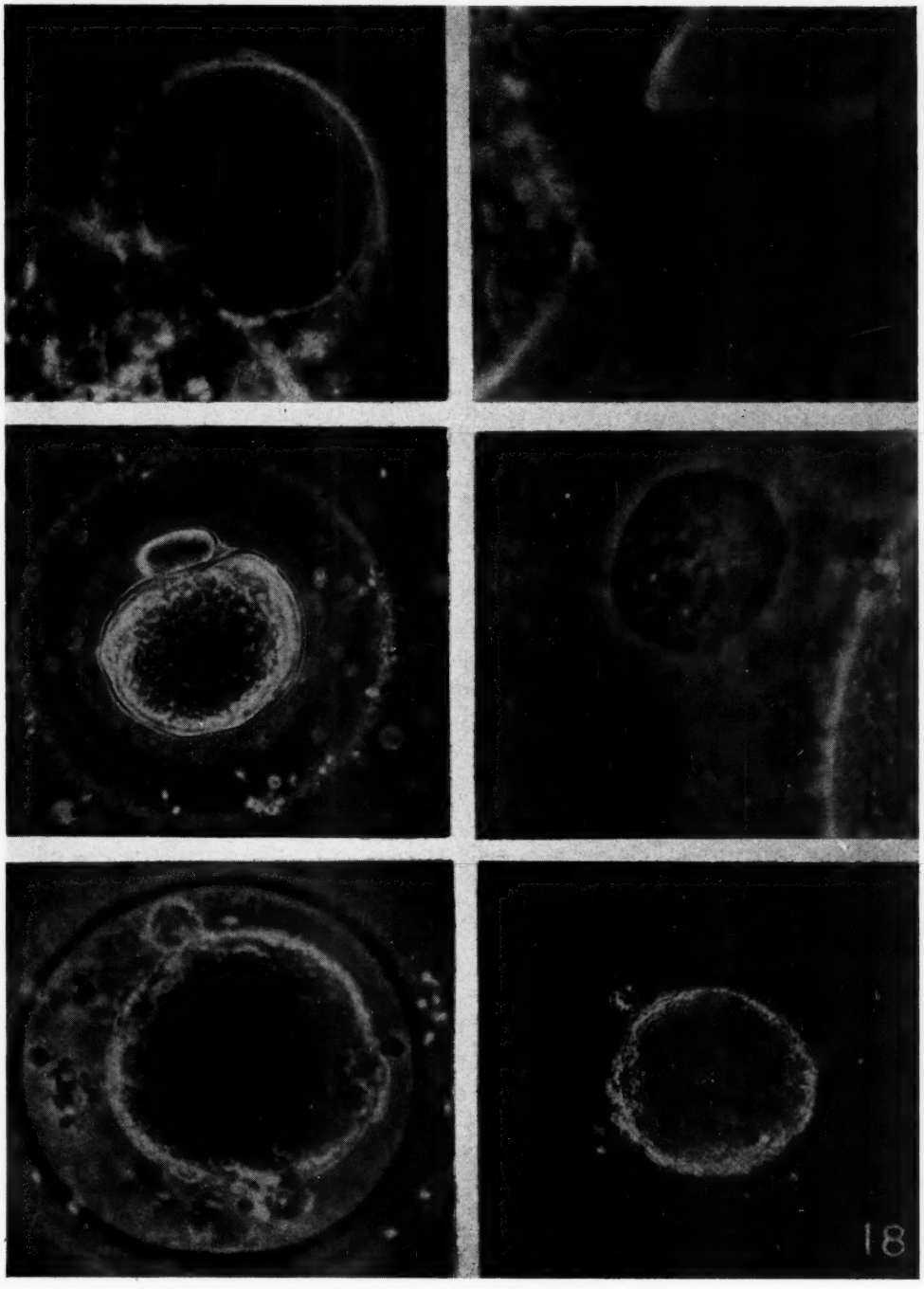

Fig. 13.—First polar body attached to follicular ovum. (×430.)
Fig. 14.—Attachment of polar body in Fig. 13. (×970.)
Fig. 15.—First polar body and spermatozoa in zona pellucida, follicular egg. (×100.)
Fig. 16.—First polar body in Fig. 15, free. (×430.)
Fig. 17.—Two polar bodies, follicular ovum. (×100.)
Fig. 18.—Two polar bodies, follicular ovum. (×160.)

free of spermatozoa. The egg with the spermatozoon still attached at a right angle to the surface of the zona pellucida was covered with a cover glass supported by a petrolatum ring. The behavior of the spermatozoon was then studied. It rotated on its longitudinal axis as its head passed into the zona pellucida. As the head was observed in focus in the equatorial plane, the rate of rotation decreased until by the time the tip of the head was midway in the zona pellucida the front and side views of the head could be seen to alternate. The progression of the head through the zona pellucida was intermittent until only the tail lay in it, at which time the head and body underwent several intermittent, side-to-side jerky movements and then the tail slipped into the perivitelline space. Within the perivitelline space, the movement was forward and intermittent but not as great as previously in the follicular fluid. The time required for this spermatozoon to traverse the zona pellucida completely was 18 minutes. It moved about within the perivitelline space intermittently until by the end of 6 hours no further movement could be detected (Fig. 10).

In Fig. 12 is shown another ovum after 24 hours of culture with a nucleus or germinal vesicle which had migrated to just beneath the vitelline membrane. It is in the process of the first maturation division, i.e., preparatory to release of the first polar body.

A first polar body that had almost completely formed in another ovum after the same period of incubation is shown in Fig. 13, the remaining attachment of which is given in greater detail in Fig. 14.

Fig. 15 represents an egg after 10 hours of incubation with spermatozoa. The egg was washed preceding photography. The first polar body was almost released and spermatozoa were present in the zona pellucida. By the end of 12 hours of incubation the polar body was set free in the perivitelline space (Fig. 16). The spiral chromosomal material can be discerned in this polar body.

First and second polar bodies were observed in the ova depicted in Figs. 17, 18, 19, and 20 after 24 hours of incubation. These preparations were also washed just before photography. Spermatozoa were present in the zona pellucida of each of these eggs, and three were in the perivitelline space of the ovum shown in Fig. 19, one of which is in sharp focus. Probable pronuclei can also be seen in Fig. 19.

The ovum in Fig. 20 shows, for the first time in the human being, the presence of three polar bodies, the first polar body having almost completely divided. This stage was observed after 21½ hours of incubation, and by the end of 24 hours the division of the first polar body was complete (Fig. 21). Greater detail of the second polar body is given in Fig. 22. The chromosomal material can be detected in each of these polar bodies, especially the spiral chromosomal threads in Fig. 22. The zona pellucida of this egg was opened (Fig. 23) with glass dissecting needles, and the ovum as well as the three discrete polar bodies teased out separately (Fig. 24). The freed ovum was washed ten times in physiological salt solution by transfer with a fine pipette, after which it was flattened somewhat under a cover glass supported by a

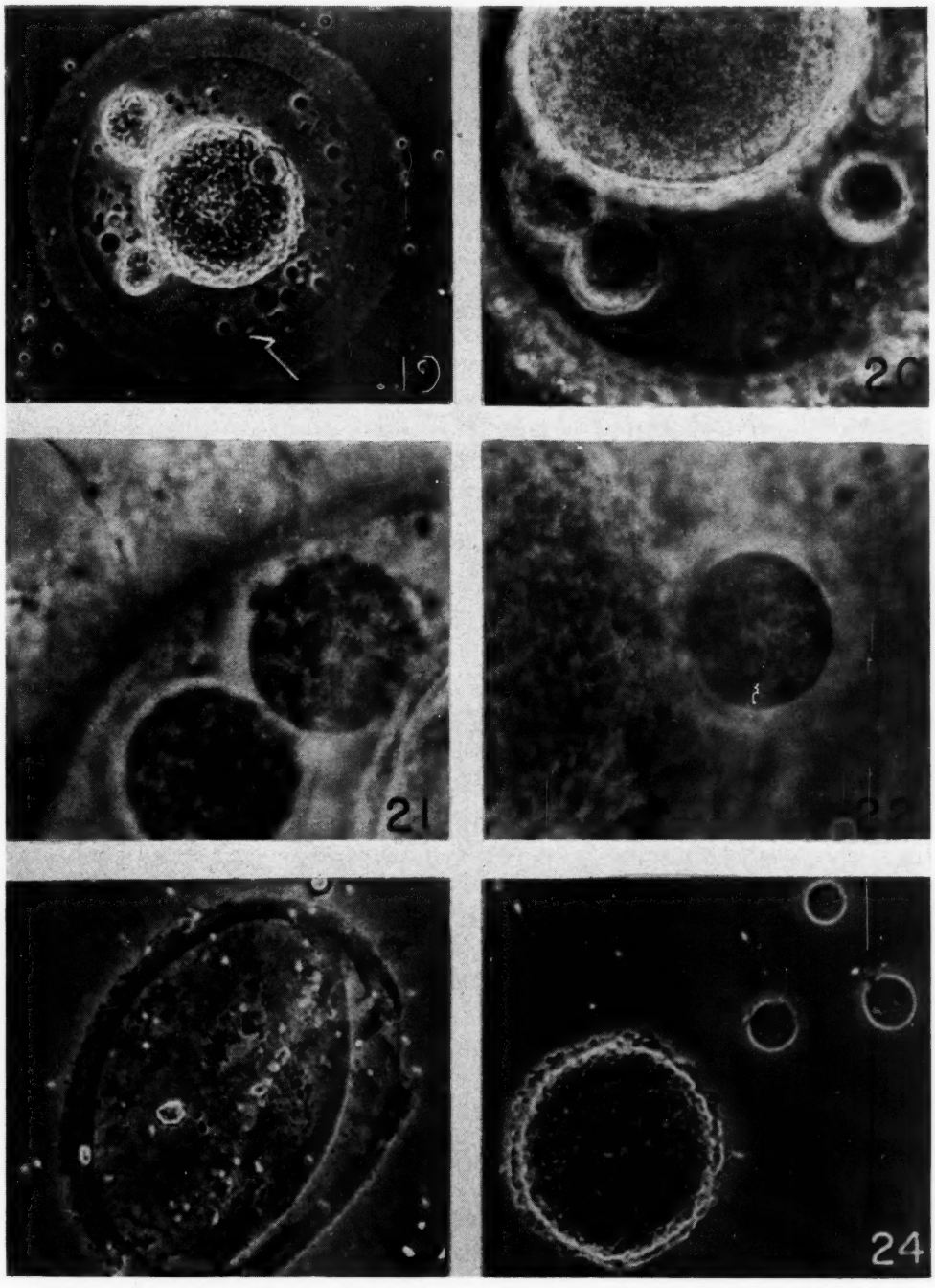

Fig. 19.—Follicular ovum with two polar bodies, spermatozoa in zona pellucida and perivitelline space; probable pronuclei. (×100.)

Fig. 20.—Follicular ovum, three polar bodies. (×200.)

Fig. 21.—Division of first polar body in Fig. 20 complete; spermatozoon in zona pellucida. (×430.)

Fig. 22.—Second polar body in Fig. 20. (×430.)

Fig. 23.—Zona pellucida from ovum in Fig. 20. (×100.)

Fig. 24.—Ovum and polar bodies in Fig. 20 without zona pellucida. (×100.)

petrolatum ring. Examination under the oil immersion phase contrast objective revealed an entire spermatozoon within the cytoplasm near the center of the egg (Fig. 25). This spermatozoon was motionless, except for active vibratile movement of the end-piece, which accounts for the ellipsoidal light area just to the right of the end of the tail. The female pronucleus was situated approximately midway between the center of the egg and its periphery. In the attempt to obtain a photograph of the female pronucleus, through the additional flattening needed to visualize it with the phase contrast, the ovum burst and the contents scattered.

Tubal Ova.—The ovum shown in Fig. 26 was obtained from a Fallopian tube removed from a patient on the fourteenth day of her menstrual cycle. The patient had regular 28-day cycles. Upon opening the abdomen and without any handling of the ovary, the point of rupture of the Graafian follicle still showed slight bright red bleeding. The corona radiata and cumulus cells are clearly shown in Fig. 26. After incubation at 37° C. for 3 hours in homologous blood serum with sermen and homologous tubal mucosa added, denudation had occurred, at which time the first polar body was clearly observed (Fig. 27). After twenty-four hours of incubation, the ovum was covered with spermatozoa until the first polar body could not be made out. The egg was washed six times with physiological salt solution and viewed again (Fig. 28). Some spermatozoa were in the zona pellucida, and others, still showing fairly active, intermittent forward progression, were within the perivitelline space. The chromatin material can be seen in the polar body (Fig. 27), partial cleavage of it having occurred (Fig. 28).

Another tubal egg with two polar bodies is shown in Fig. 29 after 24 hours of incubation, the first of which appears to have started division. This ovum was washed from a Fallopian tube removed from a patient also on the fourteenth day of a 28-day cycle. Denudation was complete by the end of 3 hours of incubation. At the end of 24 hours this ovum was also covered with innumerable spermatozoa. It was necessary to wash the egg eight times before proper visualization was achieved.

Finally, another ovum was secured from a Fallopian tube removed from a patient on the fifteenth day of her 28-day cycle. After complete denudation, spermatozoa soon covered almost the entire surface of the zona pellucida (Fig. 30). The first polar body is shown comparatively darker. The egg with the spermatozoa attached was gently transferred to a drop of homologous blood serum free of spermatozoa. The clockwise rotation continued, and at the time the photograph was taken the ovum was being rotated at the rate of 360° in 15 seconds. This rotation lasted for over 12 hours.

Comment

The partial dissolution of the corona and cumulus cells after incubation of the ovum in the follicular fluid to which fresh normal semen was added is indicative of some enzymatic action. That complete dissolution of the corona and cumulus cells was obtained after the egg was incubated in the follicular

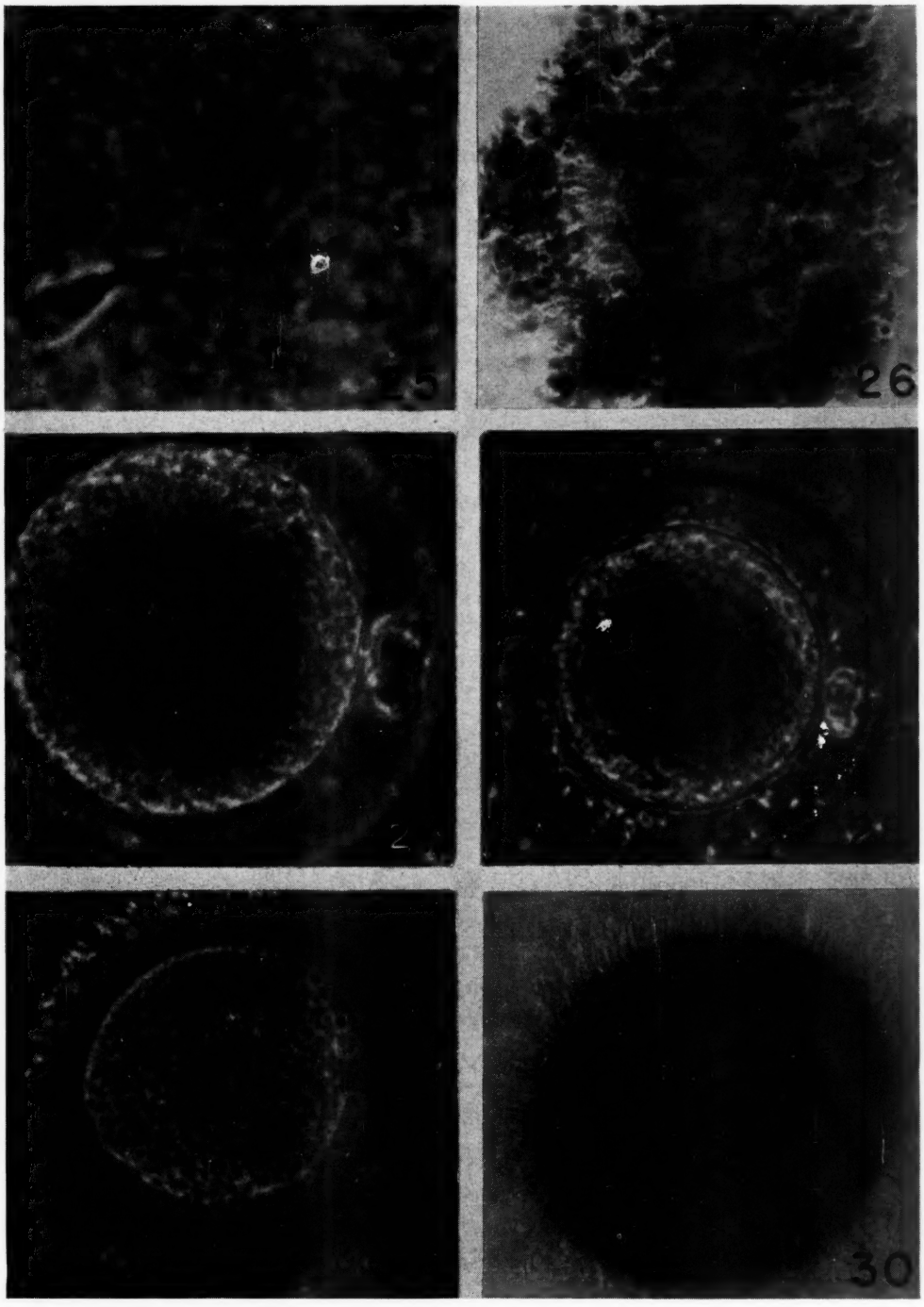

Fig. 25.—Spermatozoon in cytoplasm of ovum in Fig. 24. (×970.)
Fig. 26.—Very fresh tubal ovum. (×100.)
Fig. 27.—First polar body and denudation of ovum in Fig. 26. (×200.)
Fig. 28.—Spermatozoan penetration of ovum in Fig. 27. (×100.)
Fig. 29.—Denuded tubal ovum with two polar bodies. (×100.)
Fig. 30.—Denuded tubal ovum after exposure to spermatozoa. (×100.)

fluid or homologous blood serum to which fresh normal semen and homologous tubal mucosa were added indicates a more marked enzymatic action. It is believed that hyaluronidase is not involved since experiments with this enzyme showed no dissolution of these cells. In all probability the final action which brings about the dissolution of the corona and cumulus cells is fibrinolytic, arising from the tubal mucosa. Another factor may reside in the seminal plasma or spermatozoa, but these were not tested separately regarding denudation of the ova. It is unlikely that they are important for denudation in vivo, since denudation of normal tubal ova has been observed in the absence of spermatozoa.

The mature ovum eccentrically located within the zona pellucida seeks a fixed position as, e.g., a poorly balanced golf ball. This tendency may determine the position in which the segmented egg embeds in the uterine mucosa.

There is no evidence of trophic action of the ovum upon the spermatozoa. The spermatozoa that come in contact with the egg by chance become fixed in position around it. It is believed that the number of spermatozoa which penetrate the zona pellucida, the perivitelline space, and the ovum, and the degree to which this penetration occurs are manifestations of the activity of the respective male germ cells. The number of spermatozoa which reach and penetrate the human egg in vivo is unknown. The entrance of several spermatozoa into the perivitelline space is in keeping with the observations of Blandau and Odor[37] on rat ova. This would indicate the possibility of more than one spermatozoon penetrating the ooplasm in the human being. Why the one spermatozoon enters finally into the formation of the male pronoucleus remains unknown and may be determned entirely by chance approximation of the male to the female pronucleus.

The clockwise rotation of the ovum by the spermatozoa probably results from the effective stroke of the spermatozoan tails. Obviously, we do not know if this occurs within the Fallopian tube. If it does, the functional significance of these rotary movements of the ovum remains completely obscure.

The fibrillar network in the zona pellucida probably adds to its elasticity. This characteristic of the zona pellucida may help in maintaining the integrity of the cleaving and early expanding cellular mass. It is conceivable that tubal implantation might result from premature release of the fertilized ovum from the zona pellucida.

It is generally believed that the stimulus to the final step in maturation of the ovum, i.e., the reduction division with release of the second polar body, is the entrance of the spermatozoon into the cytoplasm of the egg. This belief is supported by the finding of an ovum with three polar bodies and with an entire spermatozoon within its ooplasm.

Since the whole fertilizing spermatozoon has been reported within the ooplasm in several other mammals, and one has been observed in the human ovum, more credit is probably due the male in regard to his cytoplasmic contribution to the offspring than has theretofore been rendered him.

Summary

1. Methods for obtaining and studying living follicular and tubal ova by means of phase contrast microscopy are presented.

2. A procedure for obtaining completely denuded follicular and tubal ova is outlined, and possible factors involved are stated.

3. Spermatozoan behavior about and penetration of follicular and tubal ova are described.

4. The constitutents of the zona pellucida and perivitelline space are shown and discussed.

5. Maturation stages of the follicular and tubal ovum are depicted, with special reference to polar body formation.

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MEASUREMENT OF UTERINE BLOOD FLOW AND UTERINE METABOLISM

IV. Results in Normal Pregnancy*

(From the Obstetric Research Laboratory and the Department of Obstetrics, University of Cincinnati and the Cincinnati General Hospital)

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IN PREVIOUS papers[1, 2] we discussed the possible application of the nitrous oxide method to the measurement of the uterine blood flow in nonpregnant and pregnant women. The techniques for obtaining samples of blood from the uterine veins and from the brachial artery were also outlined. The present paper deals with results of specific measurements obtained in normal pregnant subjects during the last month of gestation. Studies made on postpartum patients 24 to 48 hours following delivery will also be reported.

Material and Methods

The material for this study consisted of 48 normotensive patients. Of these, 30 were in the last month of pregnancy and 18 were in the postpartum period. None of the patients had any history or clinical findings of cardiovascular, renal, or pulmonary diseases. The majority were admitted to the obstetric ward not in labor for repeat elective cesarean section. The subjects studied in the postpartum period were undergoing tubal ligation for multiparity. Catheterization of the uterine vein was employed in 12 pregnant and 2 postpartum patients, according to the technique described elsewhere.[2] This technique was successful in only 3 pregnant patients and one postpartum patient. Cannulation of the uterine vein during cesarean section or tubal ligation was resorted to in 18 pregnant and 16 postpartum subjects. This technique was successful in 4 pregnant and 3 postpartum patients. The causes of this large number of failures will be discussed below. Collection of venous and arterial blood samples followed the general principles outlined elsewhere.[2] The blood samples were kept on ice throughout the procedure and were analyzed for nitrous oxide, carbon dioxide, and oxygen within 4 to 6 hours after the completion of the procedure. The concentration of nitrous oxide was plotted against time and calculation of flows was made by integration of the areas between the arterial and venous curves for the time consumed by each experiment. Estimation of the uterine blood flow was made from the formula:

$$UBF = \frac{100\ VuS}{\int_0^u (A\text{-}V)dt}$$

The oxygen consumption was estimated from the equation:

$$UMRO_2 = \frac{UBF \times (A\text{-}V)O_2}{100}$$

*This investigation was supported in part by grants from the National Heart Institute, National Institutes of Health, Public Health Service, Bethesda 14, Md.

and the uterine vascular resistance from the equation:

$$UVR = \frac{MBP}{UBF}$$

These formulas have been discussed with more details elsewhere.[1]

The mean arterial pressure was calculated by adding 1/3 of the pulse pressure to the diastolic blood pressure.

Nitrous oxide, carbon dioxide, and oxygen were analyzed in the Van Slyke-Neill apparatus according to methods described elsewhere.[3]

Results

Table I shows the results obtained in the patients studied in the prepartum and postpartum periods. In it are listed the name, number, parity, and age of the patients, the length of gestation, the procedure used in obtaining uterine venous blood samples, as well as the values for mean arterial pressure, blood flow, oxygen consumption, and vascular resistance.

Uterine Blood Flow.—

The blood flow to the uterus during the last month of normal gestation varied from 12.2 to 18.5 c.c. per 100 Gm. per minute with an average of 15 c.c. per 100 Gm. per minute. There was a slight tendency to obtain higher values with the cannulation technique than with the catheterization, but the difference was not statistically significant. Twenty-four to 48 hours following delivery the blood flow to the uterus decreased to an average of 9 c.c. per 100 Gm. per minute. Estimation of the blood flow to the entire uterus and its contents is difficult to make since there is no way to determine its weight prior to the delivery of the fetus. However, if we accept Chesley's[4] figures of 5 kilograms as being the approximate weight of the uterus, fetus, and amniotic fluid at the end of gestation, the blood flow for the entire uterus would be close to 750 c.c. per minute.

Oxygen Consumption.—

The oxygen consumption of the pregnant uterus during the last month of gestation was found to vary from 1.4 to 2.4 with an average of 1.9 c.c. per 100 Gm. per minute. Following delivery, the oxygen consumption fell to approximately 1 c.c. per 100 Gm. per minute which is one-half of the prepartum values.

Uterine Vascular Resistance.—

The resistance to the blood flow in the uterine vascular bed varied from 4.5 to 7 mm. Hg/c.c. per 100 Gm. per minute. In the postpartum period, uterine vascular resistance rose to approximately 9. The rise was caused by a decrease in the blood flow rather than by an increase in the mean arterial pressure.

Comment

For an understanding of the significance of the present set of figures, it is necessary to discuss the validity as well as the causes of error involved in the methods and techniques used.

As was mentioned previously,[1] the formula used for calculation of the uterine blood flow takes into consideration the partition coefficient of nitrous oxide in uterine, fetal, and placental tissues. This factor, which is represented by the letter *S* in the equation, has not been studied as yet. In all our calculations we assumed this factor to be equal to 1, which is the value of the partition coefficient of N_2O in brain tissue. That this assumption may not represent the true value for the pregnant uterus is suggested from the lack of adequate equi-

TABLE I.

NAME	HOSP. NO.	PARITY	AGE	WEEKS' GESTATION	PROCEDURE	MEAN ARTERIAL PRESSURE	BLOOD FLOW (C.C./100 GM./MIN.)	O_2 CONSUMPTION (C.C./100 GM./MIN.)	UTERINE VASCULAR RESISTANCE (MM. HG/C.C. PER 100 GM. PER MINUTE)
C. P.	255312	Mult.	24	40	Cannulation	83	18.5	2.2	4.5
H. W.	245766	Mult.	29	39	Cannulation	87	15.4	1.8	5.7
C. F.	280409	Prim.	16	39	Cannulation	80	17.3	2.4	4.6
B. P.	106819	Mult.	27	40	Cannulation	84	14.2	1.6	6.0
C. M.	12752	Prim.	24	37	Catheterization	88	13.7	1.8	6.4
T. B.	26538	Mult.	32	40	Catheterization	86	14.3	2.4	6.0
L. Ha.	285321	Prim.	22	38	Catheterization	86	12.2	1.4	7.0
B. Pr.	17051	Mult.	38	Postpartum	Cannulation	82	8.1	0.8	10.0
L. H.	289874	Mult.	36	Postpartum	Cannulation	79	9.3	1.0	8.5
E. J.	51895	Mult.	34	Postpartum	Cannulation	80	10.6	1.2	7.5
M. T.	39784	Mult.	37	Postpartum	Catheterization	82	10.7	0.9	7.6

librium between the N_2O tension in the venous blood and uterine and fetal tissue after ten minutes. When the N_2O method is used for the study of cerebral circulation, the arterial and venous curves draw close to each other as an asymptote after a ten-minute period. For this reason, this period is sufficient for measurement of cerebral blood flow. In the case of the pregnant uterus the curves are still far apart after ten minutes (Fig. 1), indicating that equilibrium has not as yet been achieved. In the cases reported here the inhalation of N_2O had to be continued for 20 to 30 minutes in order to obtain fairly good curves.

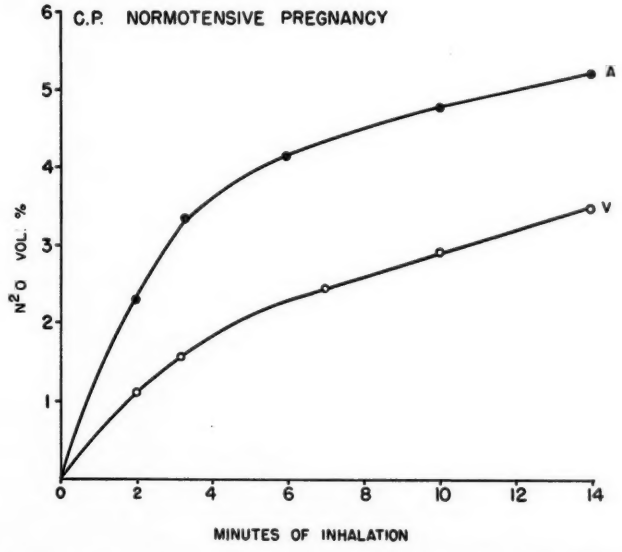

Fig. 1.—Arterial and venous concentration of N_2O are plotted against time. Note that after 10 minutes the 2 curves did not get close to each other as is observed in cerebral blood flow. It is necessary to prolong the inhalation of N_2O for 20 or 30 minutes in order to obtain adequate curves.

The need for such a prolonged period of N_2O inhalation was one of the major causes of failure in obtaining adequate studies, since in many cases of cannulation during cesarean section it was not possible to complete the procedure. The individual variations in the values of uterine blood flows during pregnancy as listed in Table I might be due to variation in the partition coefficient of N_2O. However, since this factor was neglected in all cases, it is probable that the variations are due to other interfering factors.

Location of the placenta may interfere with calculation of the uterine blood flow since, at least on theoretical grounds, the venous return from the side where the placenta is implanted should be higher than from the opposite side. In the present study the patients were taken at random without any regard to the site of the placenta, and no attempt was made to study both sides of the uterus. Therefore, it is possible that the individual variations among the pregnant patients might be due to variation in blood flows caused by different locations of the placenta. However, since the difference in the individual values does not seem to exceed what is thought to be normal variations of the method,

it is probable that the location of the placenta did not exert a great deal of influence on the calculation of the uterine blood flow. Further studies, however, are needed to confirm this assumption.

Another cause of error which might introduce a doubt as to the validity of the figures is the possibility that the venous samples obtained from the uterine veins are mixed with venous blood coming from other pelvic organs. In this case, the venous samples are not true representatives of the uterine venous blood. By the same token, a certain amount of uterine venous blood is drained through the ovarian veins and, therefore, is not included in our calculations. Although these causes of errors have not as yet been eliminated, their significance is still to be determined. The values obtained by both the catheterization and the cannulation techniques are closely similar, and it appears that both techniques yield venous samples which could be considered as representative of the same region.

On the basis of the foregoing discussion, it is only fair to state that the figures for uterine blood flow obtained in normal pregnancy should be regarded with a certain caution as representing an approximate estimate of the flow during the last month of gestation. Evidently the significance of these figures would be better assessed when more cases are studied and when most of the causes of error have been eliminated. Furthermore, the validity of the N_2O technique in the measurement of uterine blood flow would be better judged when this technique is "calibrated" with direct methods used for similar purposes in animals. In this connection, it is appropriate to mention that our average value of 15 c.c. per 100 Gm. per minute is in close agreement with values obtained by Barcroft and his associates[5] in rabbits. Using a direct method, these authors found that, in pregnant rabbits at the twenty-eighth day of gestation, the blood flow to the uterus approximates 28 to 30 c.c. per minute. If we assume that in the rabbit the weight of the pregnant uterus at that period of gestation is close to 200 grams, simple calculation would show that the flow is 15 c.c. per 100 Gm. per minute.

The same considerations are applied to the values of oxygen consumption, since their accuracy depends on that of the uterine blood flow. The figures indicate that the oxygen consumption of the pregnant uterus approximates 2 c.c. per 100 Gm. per minute and decreases to less than one-half of this value within the first few hours after delivery. Here again there is close agreement with values of 1.5 to 2 c.c. obtained by Barcroft in rabbits at the twenty-eighth day of gestation.

Regarding the results observed in the postpartum period, it is possible that the figures are closer to the true values than those obtained in the prepartum period, since the cause of error attributed to the presence of placenta and fetus is not present and a better N_2O equilibrium is achieved. Here, again, more cases are needed in order to formulate a definite opinion.

Comparison of the values obtained in the study of uterine circulation with those of cerebral circulation obtained by the same method[6] yields interesting facts. While the brain receives an average of 54 c.c. per 100 Gm. per minute in a normal subject at rest, the pregnant uterus at term receives approximately one-

fourth of this amount. However, the oxygen consumption of the brain is close to 3.3 c.c. per 100 Gm. per minute whereas that of the pregnant uterus approximates one-half of this quantity. These figures indicate that the pregnant uterus extracts much more oxygen per unit of blood flow than does the brain. It is probable that the fetus is directly responsible for this large oxygen consumption.

Of interest from the standpoint of investigative methods is the large number of failures encountered in the present study. Of 48 attempts to carry out these procedures, success was met in only 11 instances. These staggering figures serve to indicate that the method in its present status is economically and scientifically impractical. The major causes of failure were difficulties in introducing the catheter into the uterine vein within a reasonable period of time, difficulties in obtaining blood samples without air, occasional clotting of the blood samples, and difficult exposure of the main uterine venous trunk. In many cases, after the uterine vein had been properly cannulated during abdominal operation and some samples of venous blood were obtained, the procedure had to be discontinued because of signs of fetal and maternal distress. For these reasons we believe that the use of this method for studying uterine blood flow presents many difficulties and will remain a highly investigative procedure until it is improved and made more practical.

Summary and Conclusions

1. Measurements of uterine blood flow, oxygen consumption, and uterine vascular resistance were made in normal pregnancy in the prepartum and postpartum periods.

2. During the last month of pregnancy, the uterine blood flow averages 15 c.c. per 100 Gm. per minute and falls to 9 c.c. within the first 24 hours following delivery; oxygen consumption averages 1.9 c.c. per 100 Gm. per minute and falls to 1 c.c. per 100 Gm. per minute; vascular resistance averages 6 and rises to 9 mm. Hg/c.c. per 100 Gm. per minute in the postpartum period.

3. The significance of these values has been discussed.

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TOXEMIA OF PREGNANCY AND ALTERED RENAL CIRCULATION*

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WHAT is the cause of toxemia of pregnancy? Until an acceptable explanation of the etiology of toxemia is advanced, exploration of any theory which tends to correlate the confusion of symptoms, findings, and observations pertaining to the condition would appear to be justified. We believe the discussion to be presented here does contribute to such correlation and hence deserves consideration.

In order to avoid confusion and to limit discussion to the basic problem, we will use the term "toxemia of pregnancy" in its customary sense to describe the clinical syndrome appearing during pregnancy and characterized by hypertension, albuminuria, and edema. If unchecked these symptoms may progress to include vascular changes, oliguria, renal insufficiency with retention of metabolites, convulsions, coma, anuria, and other manifestations ordinarily referred to as "eclampsia" ("acute toxemia of pregnancy" as defined and classified by the American Committee on Maternal Welfare, 1952). We will disregard for the present that "toxemia" which appears to be superimposed upon pre-existing cardiovascular-renal disease.

The purpose of this paper is to invite attention to the parallel in symptomatology of "toxemia" on the one hand and the reported results of experimentally altered renal circulation on the other. It is believed that this parallel is more than a coincidence, and that the possibility of a common physiological background must be given careful consideration.

In order to focus attention upon this possible relationship we would like to ask the following hypothetical question: If in the course of pregnancy conditions develop which significantly interfere with renal circulation, what symptoms would we anticipate and what would be the clinical character of the resulting symptom complex?

For the answer to this question let us turn to the published reports of certain investigators who have worked on the problem of altered renal circulation and see what, if any, of their findings fit into the "toxemic" picture.

Hypertension

Hypertension is a primary sign of toxemia. The severity of the disease tends to vary directly with the degree of elevation in blood pressure. In "true toxemia"—that not superimposed on previous kidney or vascular disease—one expects the hypertension to subside following delivery. This close parallel of

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symptom and disease is of particular interest when we review the observations made in connection with the experimental production of renal hypertension.

A great amount of experimental work involving the kidney and its function has been directed toward the problem of etiology in essential hypertension. This literature need not be reviewed here except for those conclusions which pertain to our present discussion, that is, "altered renal circulation."

Goldblatt[1] discussing the experimental production of hypertension states: "Compression of the kidneys by an oncometer had been tried, in 1909 by Alwens, who reported slight immediate elevation of blood pressure in some brief experiments in cats. More recently, a similar effect on the kidney of a persistent type has been produced by Page and Collaborators (1939) by the envelopment of the kidneys in cellophane or silk. The same effect has been obtained in rats and dogs (Greenwood, Naiser and Taylor, 1939; Hermann, Jourdan and Vial, 1940) by means of collodion painted on the surface of the kidneys and also by compression of the kidneys by means of a tape tied in a spiral form around the kidney (Grollman 1944). These methods are supposed to act by direct compression of the kidney substance or by the compression and resultant ischemia caused by the thick perirenal scar which results from the perinephritis induced by the foreign material."

Braun-Menendez,[2] however, states, "To Goldblatt, Lynch, Hanzel and Summervill (1934) is due the credit of demonstrating conclusively that localized ischemia of renal tissue is capable of producing persistent hypertension in the dog." The method employed by Goldblatt involved constriction of the renal arteries by an appropriately placed clamp, the results obviously being due to the resulting alteration in renal circulation.

Then again, Goldblatt[1] states, "In the light of our own experiments it appears probable that occlusion of an ureter may produce a hemodynamic disturbance similar to but not as pronounced as the effect of constriction of the main renal artery." He states further, "Passive hyperemia of one kidney produced by the constriction of the main renal vein had been reported by Pendersen in 1927, as causing a transient elevation of blood pressure in the dog. This has been confirmed by Braun-Menendez (1933), Dicker (1937) and Friedberg (1944)."

The common factor in all of these observations has been elevation of the blood pressure induced by means of altered renal circulation.

Furthermore, it has been demonstrated experimentally that hypertension is not only one of the first signs of altered renal circulation but that it appears quite independent of any other evidence of impaired renal function. As stated by Goldblatt,[1] "It was shown, therefore, experimentally, that merely by disturbance of the intra-renal hemodynamics, hypertension was produced, which, although obviously of renal origin, nevertheless had no accompanying disturbance of renal excretory function."

Page and Corcoran[3] state, "Several different aspects of renal function can thus be maintained at normal levels during the course of experimental renal hypertension. These are (a) renal blood and plasma flow; (b) glomerular

filtration rate and (c) tubular secretory capacity for such substances as diodrast. It must therefore be concluded that renal pressure (giving rise to hypertension) and excretory activity are completely dissociated. . . . However, because both types of function occur in the same organ, it is not surprising that the local renal disorders which affect the one commonly affect the other.''

On the basis of the evidence cited one is, we believe, justified in concluding that altered renal circulation may result in hypertension. This hypertension, although unquestionably of renal origin, may be accompanied by no evidence of abnormal renal excretory function or demonstrable reduction in renal blood flow.

Albuminuria

Albuminuria is almost as constant a symptom of toxemia as hypertension. The amount varies with the severity of the disease. The association of albuminuria and changes in renal circulation has been repeatedly observed. In discussing ''benign albuminuria'' Fishberg[4] states, ''At the height of the albuminuria there is more or less marked oliguria and usually a diminution in chloride content of the urine, the other urinary constituents being present in normal amounts. These changes are those which would be expected in slight circulatory stasis.'' Further, after quoting reports of albuminuria found consistently in healthy college athletes following vigorous exercise, he states, ''The mechanism producing the albuminuria is not precisely known, but it seems very probable that it results from circulatory changes in the kidneys. Exercise, cold bathing, fright and mental strain all produce vasoconstriction as manifested by rise in blood pressure. During violent exercise such as crew races, there is also increase in the intra-abdominal pressure which may interfere with the venous return from the kidneys. It is known from animal experimentation how readily even transitory interference with either arterial or venous supply to the kidney produces albuminuria.''

King and Gronbeck[5] state, "Cases [of albuminuria] have been reported associated with enlargement of abdominal viscera presumably due to pressure upon the renal circulation. The variable albuminuria of pregnancy without renal disease or toxemia may be of similar origin. . . . Under conditions of strain, imposed by various positions, interference with renal circulation and function results in albuminuria."

Further evidence along this line has been published by Bradley and Bradley.[6] They placed human subjects in ''G'' suits, by means of which an average increase of intra-abdominal pressure of 20 mm. Hg was produced. The effective renal blood flow was thereby greatly reduced.

They state, ''It has been repeatedly demonstrated that reduction of renal venous drainage is associated with the appearance of proteinuria. Abdominal compression gave variable amounts. It occurred regularly.''

In the light of these observations, then, one would appear to be justified in saying altered renal circulation can cause albuminuria.

Edema (Salt and Water Retention)

Altered renal circulation can apparently also be a factor in the retention of salt and water with the resulting clinical finding of edema.

Bradley and Bradley[7] by applying external pressure to the abdomens of normal subjects were able to demonstrate not only a reduction in renal blood flow, but also depressed glomerular filtration, and decreased excretion of sodium, potassium, and water. They state, "Increased intra-abdominal pressure appears to induce a renal retention of water and electrolytes. . . . Augmented tubular reabsorption of water and sodium may account for disparities between changes in filtration and sodium and water excretion observed in some subjects." All values returned to normal upon release of the pressure, indicating the functional nature of the process.

Thorington and Schmidt[8] report that distention of the abdominal cavity in experimental animals gave oliguria with pressures of 15 mm. Hg, anuria with 30 mm. Hg. They point out that a tense accumulation of ascites may be associated with oliguria, which disappears following paracentesis, and state, "The intra-abdominal tension required to produce a diminution in urinary output is not great. Two patients whose intra-abdominal tension was measured by means of a trocar and attached mercury manometer registered 15 and 20 mm. Hg."

Bradley[6] reports a subject with diabetes insipidus who presented marked diuresis as a result of Pitressin withdrawal, and who became oliguric with abdominal compression.

Cargill[9] states, "Increased intra-abdominal pressure results in a failure normally to excrete injected sodium chloride solution."

These observations have the one conclusion in common, that is, altered renal circulation may interfere with the normal excretion of salt and water by the kidneys.

In the light of this brief review of the findings which accompany altered renal circulation, we are in a position to answer our original question. We can state that, if during the course of pregnancy conditions develop which significantly interfere with renal circulation, we should anticipate the development of hypertension, albuminuria, and edema. Any pregnant woman presenting this symptom complex would unquestionably have a diagnosis of toxemia of pregnancy.

The symptoms discussed so far, hypertension, albuminuria, salt and water retention (edema), are, we believe, the primary symptoms of toxemia. These same symptoms have been observed clinically and have been demonstrated by animal and human experimentation to occur when factors interfering with renal circulation are present. Furthermore, it would appear that they may be present without evidence of impaired renal excretory function, demonstrable reduction in renal blood flow, or changes in blood chemistry. They disappear when renal circulation again becomes normal. Being purely functional manifestations one would anticipate no histological changes at this stage.

Secondary Symptoms

Certain other symptoms appearing in toxemia patients, we believe, represent a later or more advanced stage of the same process.

Hypertension is the primary manifestation of peripheral vascular constriction. If severe and of sufficient duration this constriction may bring about secondary vascular changes and lesions. For example, Keyes and Goldblatt[10] demonstrated that experimental hypertension produced retinal changes. They state, "The disease process in the small arteries of the retina varied from simple hypertrophy and hyperplasia of the muscle to advanced hyalinization of the intima and atrophy of the media." Extensive and recurrent hemorrhages were observed in the retinal vessels. Detachment of the retina was observed which they considered due to retinal and subretinal edema.

Referring to clinical toxemia Fishberg[4] states, "Hypertensive-neuro-retinopathy due to toxemia of pregnancy is more apt than other forms of this retinal lesion to be complicated by detachment of the retina; this is probably due to the general water retention favoring the accumulation of fluid behind the retina."

Dieckmann[11] recognized no specific pathologic lesions characteristic of toxemia. However, he points out that edema, capillary hemorrhages, and thrombosis are frequently seen. In the liver this is seen as a portal thrombosis, necrosis, and hemorrhage. Multiple minute hemorrhages and at times massive hemorrhage are found in the brain. The kidneys may be deep red but are usually pale and small hemorrhages may be seen. This vascular impairment incident to late toxemia might explain the uterine or placental hemorrhages and placental infarctions which have been observed in association with toxemia at times.

Eclampsia, by which is meant convulsive seizures associated with toxemia of pregnancy, is assumed to be a seriously advanced stage of the same process.

Fishberg[4] states, "There can be no doubt that eclampsia is merely one of the culminations of the hypertensive toxemia of pregnancy. . . . Eclampsia differs in no wise from the epileptic-form seizures that may occur in glomerulonephritis or in the malignant phase of essential hypertension. In all these conditions—glomerulo-nephritis, the malignant phase of essential hypertension and the toxemia of pregnancy—when the diastolic pressure reaches a very high level, it may produce edema of the brain and through the latter headache, convulsions, cerebral vomiting, amaurosis, and other manifestations which are gathered under the name of hypertensive encephalopathy.

"While the primary factor in the production of the edema of the brain which is manifest by eclampsia is pronounced diastolic hypertension, it seems probable that the water retention characteristic of the toxemia of pregnancy is an accessory factor."

Fishberg[4] states further, "There are no known changes in blood chemistry characteristic of hypertensive encephalopathy. If renal insufficiency is also present—which is often, but far from always the case—the characteristic chemical findings in the blood will be found. In other cases, however, the blood chemistry is normal throughout until either recovery or death. . . . The fact

that there is no direct correlation between retention of urinary constituents and hypertensive encephalopathy cannot be too strongly emphasized.''

The discussion then has produced evidence to show that altered renal circulation can result in a triad of symptoms consisting of hypertension, albuminuria, and edema. These changes as they develop further may result in generalized edema, peripheral vascular lesions, convulsions, and coma.

As has already been stated, these symptoms may develop without any evidence of impaired renal excretory function. With increased embarrassment of the renal circulation, however, azotemia with accompanying blood chemistry changes may develop, oliguria or anuria and histological changes in renal tissue can be anticipated.

It would appear therefore that altered renal circulation, if present, could explain the entire clinical syndrome known as acute toxemia of pregnancy.

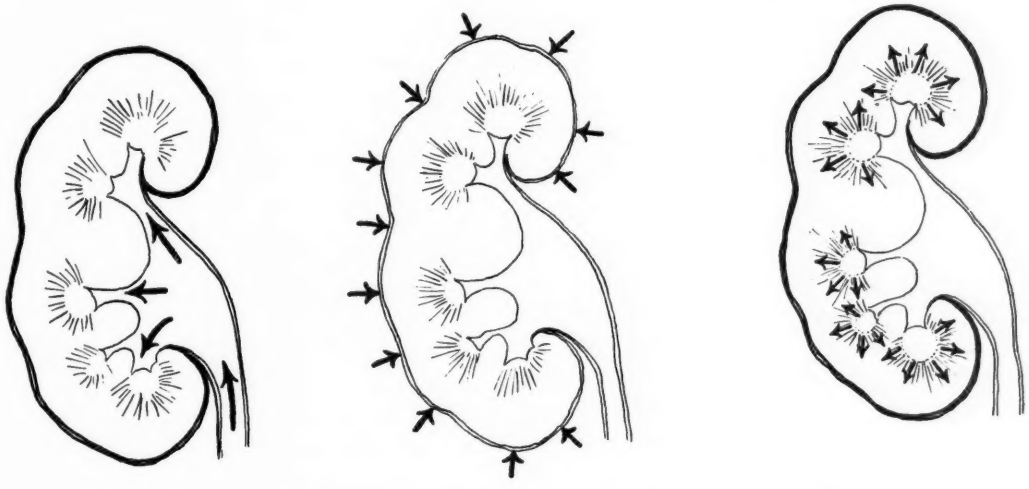

Fig. 1. Fig. 2. Fig. 3.

Fig. 1.—Diagram illustrating the concept that ureteral back pressure into the kidney pelvis could contribute to renal tamponade. The capsule limits outward expansion of the renal parenchyma.

Fig. 2.—Diagram illustrating the concept of renal tamponade by extrarenal compression of the kidney.

Fig. 3.—Diagram illustrating the concept of swelling within the kidney substance which theoretically could limit circulation through the renal tissue.

Theory as to Mechanism

We must now consider the mechanism which might result in a pregnant woman presenting the symptoms of altered renal circulation, that is, toxemia of pregnancy. It is not the purpose of this paper to review the details of renal anatomy and physiology. However, it will be necessary to point out certain facts which may have a bearing upon the present discussion.

In the first place, it should be noted that the kidney is a fleshy organ, the substance of which is made up almost entirely of hollow or tubular structures: arteries, arterioles, capillaries, veins, glomerulae, renal tubules, and renal pelvis.

Second, the kidney is surrounded by a fibrous capsule which limits the expansion of the organ making tamponade of the renal substance possible from either ureteral back pressure or internal edema. Finally, neither the capsule, nor the kidney substance itself, offers any protection against compression of the parenchyma should the organ be subjected to any significant external pressure.

Obviously any tamponade or compression of the kidney substance, whether it be external, internal, or intracellular (Figs. 1, 2, and 3) would tend to interfere with the free flow of fluids through these hollow, compressible structures. The adequacy of the renal circulation, therefore, becomes a function of the degree of compression to which the kidney parenchyma is subjected. This may be entirely independent of nervous or glandular control since obviously vasodilatation cannot restore normal blood flow through vessels already narrowed or occluded by direct mechanical compression.

It seems, therefore, that renal function, including the entire mechanism of the humoral control of the peripheral vascular bed, proteinuria, salt and water retention, and ultimately azotemia, vascular changes, and convulsions, is at the mercy of any force which tends to compress the renal parenchyma, directly or indirectly thereby producing a condition of altered renal circulation.

Some of the possible mechanisms of this interference with renal circulation could be:

1. Direct renal compression by retroperitoneal or intra-abdominal masses, including perirenal fatty tissue or tumors.

2. Generalized increase in the intra-abdominal pressure due to tumors, ascites, pregnancy, etc. A resistant abdominal wall or wearing a tight corset would increase this hazard.

3. Internal tamponade of the kidney due to resistance to urinary flow as in compression or obstruction to the ureter with hydrostatic back pressure into the renal pelvis.

4. Interstitial compression of renal tissue due to edema within the kidney substance which could occlude terminal arterioles, capillaries, and veins. This could be the result of inflammation as in acute glomerulonephritis or pyelitis with inflammation of adjacent tissue. Edema could also result from salt retention (or excessive intake) or be due to circulatory stasis from venous back pressure. But, regardless of cause, one would expect edema of kidney substance to give compression of vessels with altered renal circulation; hence, hypertension, albuminuria, and further salt and water retention.

5. As already mentioned, compression of renal veins would alter the blood flow directly, and by contributing to renal edema.

6. Interference with the arterial supply we know will produce hypertension, as has been demonstrated by Goldblatt and others in the laboratory.

7. Tumors, cysts, or scar tissue within the kidney substance, by compression of kidney tissue, would be expected to give altered renal circulation, in proportion to the extent of involvement, as well as to the speed of development.

This list is not intended to exhaust all the possibilities. In any given situation there may be several of these factors functioning simultaneously. The

kidneys are obviously subject to various and varying temporary and perhaps permanent pressures. To practically all of them the body can presumably make adequate adjustment. It is only the occasional instance which exceeds the limits of physiologic reserve which manifests itself clinically.

As has already been pointed out, this triad—hypertension, albuminuria, edema, etc.—may be far advanced without evidence of impaired renal excretory function, yet this in no way invalidates their renal origin.

In addition it must be realized that altered renal circulation may, but does not necessarily, imply a reduction of renal blood flow. It appears to have been demonstrated experimentally that the renal blood flow may remain unchanged after constriction of the renal artery and development of hypertension in dogs. Page and Corcoran[3] concluded that it is possible to obtain hypertension by constriction of the renal parenchyma by perinephritis without constant or persistent functional renal changes and hence presumably without renal ischemia. They suggest that diminution of pulse pressure might be the factor responsible for elevation of blood pressure.

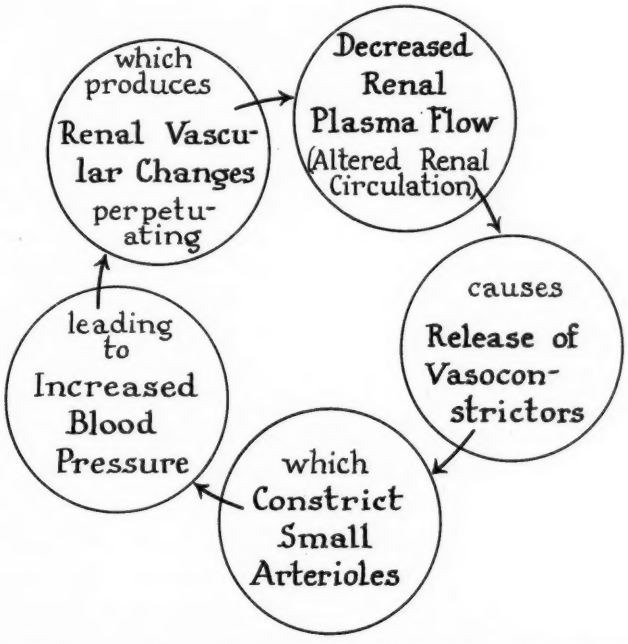

Fig. 4.—Schematic diagram of the possible self-perpetuating relationship of altered renal circulation and hypertension. (After Ciba.)

Alpert and Thomas[12] (1940) also concluded that renal blood flow may remain normal in animals with experimental renal hypertension.

Schroeder and Steele[13] observed that the blood flow returned to its normal level within a few minutes of compression unless the constriction was extreme. Hence, the presence or absence of obvious "renal ischemia" is not important. Nor is the ultimate mechanism by which altered renal circulation produces hypertension, albuminuria, salt and water retention pertinent to the present

discussion. The important point is the realization that these symptoms can be so produced.

Experimental evidence leaves little doubt that hypertension which follows altered renal hemodynamics is brought about by a humoral factor. This is quite independent of nervous control as shown by Goldblatt.[1]

Brust, Assali, and Ferris[14] state, "The results suggest that the hypertension of toxemia of pregnancy is maintained by an excessive degree of humoral tone," the accepted theory being that the kidney substance which is functioning under the handicap of altered renal hemodynamics elaborates a substance (renin) which is capable of initiating a chain of events, the end result of which is peripheral vascular constriction with its accompanying elevation in the systemic blood pressure (Fig. 4). As for the relationship of these observations to toxemia, Eastman[15] states, "The belief is growing that eclampsia is not a disease of the liver, or of the kidneys or indeed of any special organ, but of all the small arterioles. In the present state of our knowledge the best explanation of this vascular process is that it is initiated by widespread vasospasm." The evidence presented would seem to offer an explanation of the possible origin of this "widespread vasospasm."

Posture

We have endeavored to establish in the foregoing discussion that, if there were altered renal circulation of significant degree in a pregnant woman, its manifestation would be a symptom complex indistinguishable from toxemia of pregnancy. We must now consider the question, if toxemia of pregnancy is a clinical manifestation resulting from altered renal circulation, what explanation might there be for such altered renal circulation in the pregnant woman, and why is the condition seen exclusively in the human female?

Obstetrical writing is in agreement that pre-eclampsia-eclampsia is a disease peculiar to the pregnant woman. In summarizing a recent conference on "Toxemias of Pregnancy, Human and Veterinary," Browne[16] states, "After listening to this discussion, I think we shall all agree that 'toxemia' in cattle is a different disease altogether from that in woman. There is no hypertension, no edema, and there are no fits."

We believe that the most significant factor predisposing to toxemia of pregnancy in women is erect posture. Johnson[17] states, "Eclampsia occurs only in the human female, and she alone of all mammals maintains an upright position. The frequency of varices in the lower part of the body of any human being suggests that there is still imperfect adaptation to this position."

When we consider ways in which posture could affect renal circulation, it is obvious that in all quadrupeds the kidneys are located at the highest part of the intra-abdominal space. The ureters also are so located that they avoid compression by pelvic viscera or uterine mass (Figs. 5 and 6). As pregnancy develops in the quadruped female the heavy gravid uterus falls forward and down so that it is carried as in a hammock by the muscles of the abdominal wall. Pressure is not brought to bear on any major vessels or vital structures. It is reasonable to assume that there would tend to be a progressive decrease

in pressure on the kidneys, renal arteries, renal veins, and ureters during pregnancy in the quadruped female.

On the other hand with the erect posture such is not the case. The anatomical relationships to the force of gravity are reversed. Instead of the grow-

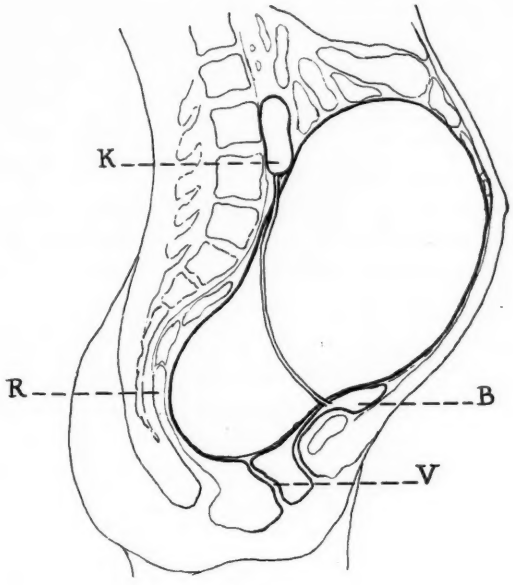

Fig. 5.

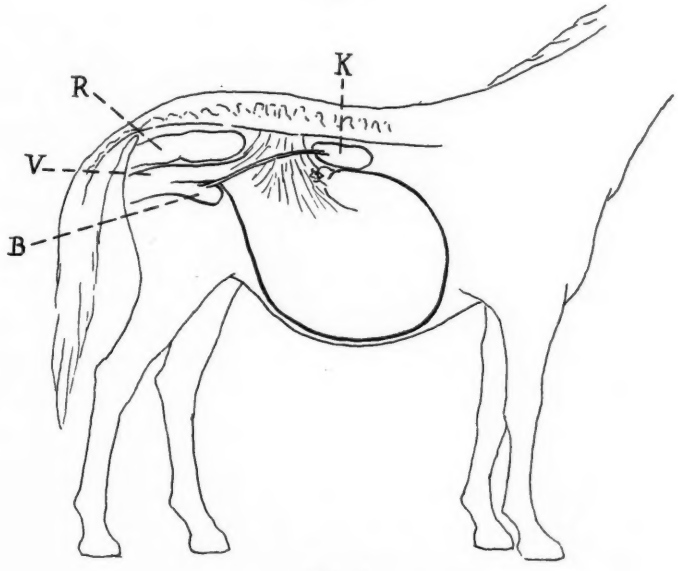

Fig. 6.

Figs. 5 and 6.—Outline drawings to point out the relationship of the pregnant uterus to the urinary tract in the upright (Fig. 5) and quadruped (Fig. 6) positions.

ing uterus falling away from the pelvic inlet as in quadrupeds it rests in the inlet with the inherent possibility of ureteral compression. Later in pregnancy as the gravid uterus goes higher in the abdominal cavity the intra-abdominal

pressure increases, the abdominal musculature tends to throw the uterus back against the spine with a correspondingly increased possibility of direct renal compression as well as possible pressure on the renal arteries and veins.

Dieckmann's[11] analysis of the frequency of toxemia among people throughout the world could be interpreted as illustrating this point. He states, "Eclampsia, toxemia, hyperemesis gravidarum and abruptio placentae are either unknown or are very rare among the native women where habits and diet have not been changed by the white race. In contrast, eclampsia is very common where natives have adopted many if not all of the diet and other habits of the white race." But we must remember that the native woman under primitive conditions has no chairs or tables, she prepares food and does her work on the floor of the hut, she washes clothes kneeling by a stream, she normally spends much of her time in at least a semiquadruped position which would tend to place her in a postural category similar to the quadrupeds, where as has been pointed out the disease does not exist. More complete assumption of the erect posture would seem to be the most significant habit of the white race to be adopted by these primitive women. Lacking a background of racial adaptation to this posture, one might anticipate an even greater incidence of toxemia among these recently primitive people than among those with a hereditary background of many generations of more complete assumption of erect posture. This apparently is true.

The possible importance of posture to this problem is also indicated by the observations of Janney and Walker, quoted by Dieckmann.[11] They studied water excretion and report a gradual reduction during pregnancy. This delayed excretion was most marked in toxemic patients. When the same patient was tested in the dorsal, sitting, Trendelenburg, and horizontal-side positions, it was found that the horizontal-side position resulted in a much better urine excretion than any of the other positions.

Pressure

The recognized factors in increased incidence of toxemia are also factors that would favor increased intra-abdominal pressure and pressure on the kidneys with accompanying altered renal circulation. The accepted observations of the higher incidence of toxemia in primigravidas, in cases of multiple pregnancy, polyhydramnios, and hydatid mole, and in patients with excessive weight gain illustrate this point.

On the other hand, those conditions which have been observed to result in the clinical improvement of toxemic patients are factors which we can assume would reduce the pressures against which the renal circulation must function. Bed rest, muscular relaxation, low salt intake, reduction of edema, rupture of membranes may be of benefit. The most effective treatment of toxemia, however, is emptying of the uterus. Except for those severe cases where there is reason to assume internal tamponade of the renal parenchyma by edema, or where secondary pathological changes in the brain, liver, or kidneys have already taken place, one can anticipate early and rapid recovery once the uterine mass has been reduced.

Edema

Salt and water retention which manifests itself as edema has been shown to result from altered renal circulation under certain experimental conditions. If the possibility of altered renal circulation in certain pregnant women is conceded, we have a reasonable explanation of the clinical and experimental response of toxemic women to the administration or restriction of salt. I would like to suggest that edema is of clinical interest but relatively unimportant except in so far as it involves two structures, namely, the brain, and the kidneys.

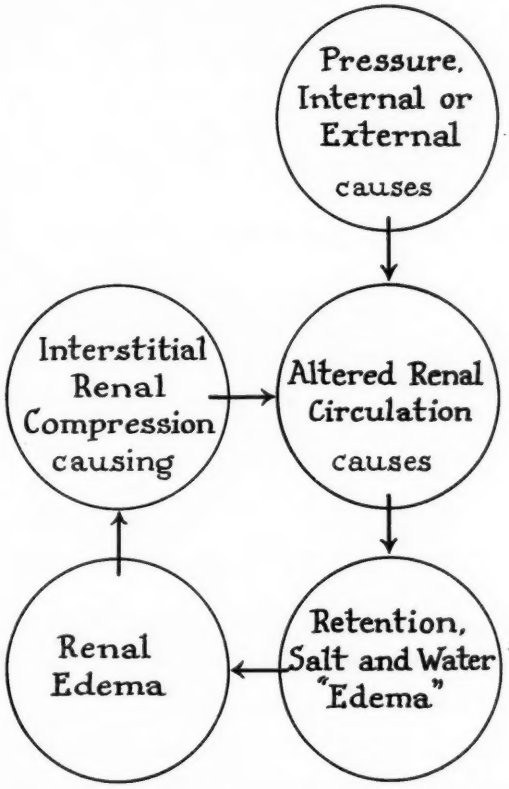
Pressure, Internal or External causes
Altered Renal Circulation causes
Retention, Salt and Water "Edema"
Renal Edema
Interstitial Renal Compression causing

Fig. 7.—Schematic diagram of the possible vicious cycle of pressure, altered renal circulation, and edema within the renal parenchyma.

In the former it can contribute to convulsions, coma, and death. In the kidneys edema within the parenchyma can cause direct compression of the renal vascular bed thereby completing a vicious cycle of pressure—altered renal circulation—oliguria—salt and water retention—renal edema—interstitial renal compression, further altered renal circulation, more edema—etc., etc. (Fig. 7).

Salt intake should theoretically increase the renal edema, and thus add to the toxemic symptoms. Evidence in favor of such a theory is found in a report by Dieckmann[18] that "the intravenous injection of 1,000 ml. of 2.5 per cent solution of sodium chloride in pre-eclamptic patients on two or more successive days caused marked increases in blood pressure, weight, and especially proteinuria.

Some patients have developed symptoms suggestive of imminent eclampsia and possibly one patient developed convulsions and coma (eclampsia) as a result of the injections.''

Limiting salt, on the other hand, should tend to counterbalance the ill effects of its retention. Clinical experience seems to confirm this expectation.

The mechanism, therefore, would appear to be that pregnancy and the erect posture give the combination of circumstance whereby, in a small percentage of cases, there is appreciable alteration of renal circulation. This possibility is increased by those mechanical factors which tend to raise intra-abdominal pressure. Faulty elimination of salt and water, on the other hand, gives a vicious cycle of salt retention and edema which further interferes with renal circulation.

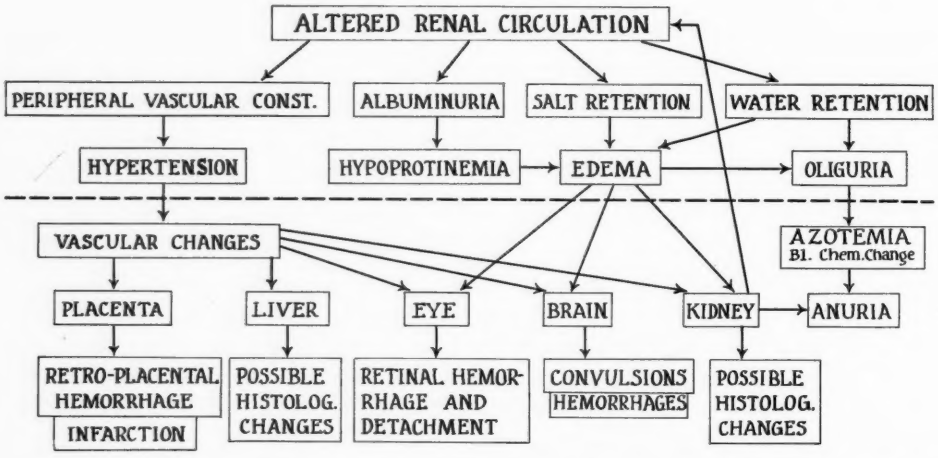

Fig. 8.—Diagram of theoretical relationship of various factors in toxemia of pregnancy. The primary symptoms (above broken line) are the result of altered renal circulation of moderate degree. At this level the changes are physiological and completely reversible. Prolonged or more severe interference with renal circulation would give increase in these signs plus vascular changes, hemorrhages, and azotemia, going on to irreversible histological changes, convulsions, and anuria.

The various forces acting on the kidneys both directly and secondary to tissue edema are visualized as varying in intensity from a subclinical degree in the great majority of pregnant women to the sudden renal suppression occasionally seen as acute fulminating toxemia. Between these extremes are those borderline cases where the presence or absence of clinical toxemia may depend on certain secondary factors.

For example, clinical observations have suggested that diet, climate, various steroids or hormones, and certain other factors may play a part at times in the incidence of toxemia. In connection with the theory presented it appears very plausible that these secondary factors could be of significance in shifting the response in certain borderline cases into the area of clinical toxemia.

The normal response to altered renal circulation, as demonstrated experimentally, is hypertension, proteinuria, and edema. In a pregnant woman this is toxemia. It is then but a matter of the degree of interference with renal

circulation between the physiological response as seen in mild pre-eclampsia and the pathological manifestations of eclampsia which are assumed to be accompanied by severe interference with or even suppression of renal circulation.

We believe that the theory presented gives an adequate working hypothesis as to the etiology of toxemia of pregnancy (Fig. 8).

Summary

1. A theory is advanced that "toxemia of pregnancy" is a "postural disease." It is unknown in quadrupeds and appears infrequently among primitive people who normally spend much of their time in a semiquadruped position. The mechanism would appear to be that in the erect position, the forces of gravity on the abdominal and pelvic organs being reversed, the gravid uterus may give increased intra-abdominal pressure, direct pressure on the kidneys, compression of renal vessels, and pressure on the lower urinary tract. The result of these forces individually or in combination would tend to cause altered renal circulation.

2. Experimental evidence has demonstrated that altered renal circulation if present can cause:

A. Hypertension, by a humoral mechanism.

B. Proteinuria, which is known to appear with renal circulatory change.

C. Edema, which is the clinical result of salt and water retention.

This triad appearing in a pregnant woman is toxemia.

In the primary phase these symptoms represent only the functional response of the body to mechanical interference with renal circulation. They may be present without impairment of renal function or demonstrable change in renal blood flow.

3. With more severe interference with renal circulation these primary symptoms may progress to include:

A. Severe hypertension, coma, and convulsions.

B. Oliguria with azotemia which may go on to anuria and uremia.

C. Generalized edema with its added effect on kidneys and brain.

D. Hypertensive vascular changes with hemorrhages and necrosis, including histologic changes in the kidneys and liver which are sometimes found at autopsy in fatal cases.

4. Treatment should be directed toward the improvement of the renal circulation, that is, the removal of the external and internal renal tamponade. Postural exercises may be of some value. Limited salt intake will tend to reduce the compression caused by interstitial renal edema. Peripheral vasodilating drugs or procedures may be temporarily beneficial, but real improvement can be anticipated only when the uterus is emptied and unimpaired circulation is re-established to the renal parenchyma.

5. Quadruped locomotion, the logical prophylaxis, appears impractical.

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HABITUAL ABORTION: A RADIOGRAPHIC TECHNIQUE TO DEMONSTRATE THE INCOMPETENT INTERNAL OS OF THE CERVIX

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OVER the years the problem of abortion has been of foremost interest in the minds of obstetricians and gynecologists. Most of the investigative work has concerned itself with first-trimester abortion. However, only recently some data have accumulated to indicate that anatomic defects of the cervix in the region of the internal os are a major etiological factor in abortions occurring during the second trimester. This paper has been prepared to present a radiographic technique for assessing such anatomic lesions of the cervical canal and to discuss the correction of such lesions.

Literature

In January, 1950, Lash and Lash[1] discussed and described the incompetent internal os of the cervix as a prominent etiological factor in second-trimester abortion. They indicated that this defect may vary in extent and that the fate of a subsequent pregnancy will be a function of the extent of the injury. A technique for surgical correction, first undertaken as early as 1941, was described. Palmer and Lacomme[2] in 1948 presented the question of "gaping" of the internal orifice of the cervix as a cause of repeated second-trimester abortion. They reported a single case of a woman who had suffered deep cervical tears during her first delivery and who subsequently had three second-trimester abortions. Prior to the third abortion, hormonal studies were normal. Surgical reconstruction of the uterine isthmus and the cervix was performed, following which the patient delivered a full-term infant. Douay, in discussing Palmer's report, described another and similar case of his own in which surgical repair was carried out successfully.

In 1950 Palmer[3] performed monometric hysterography on a series of patients. His findings indicated that anatomic variations of the cervix may occur either on the basis of uterine anomalies or secondary to childbearing.

Fisher,[4] in 1951, reviewed the effect of amputation of the uterine cervix on childbearing. He concluded that operations of the Sturmdorf type were relatively benign in so far as future childbearing is concerned. However, both his review of the literature and his own reported cases of childbearing following extensive cervical amputation disclose a dramatic increase in the rate of premature delivery and late abortion.

Investigative Technique

The radiographic technique used is best described in two parts.

1. The Balloon Technique.—Balloon studies are very simple and revealing. The instrument used is a Best-Mixter cannula modified so that the outer caliber is the same throughout. A small balloon is attached to the tip of the cannula. Because of the variations in size of the uterine cavity and because of the variation in extent of the deformity of the area of the internal os, it has been found expedient to have three or four vari-sized balloons available (Fig. 1). Urokon is used as the radiopaque substance of choice since fluidity is essential for the contrast medium to flow freely through the system. The technique is as follows: The cervix, exposed by a speculum, is grasped on the anterior lip with a tenaculum. The balloon is inserted into the uterine cavity guided by a uterine sound. It has been our experience that if a great deal of difficulty is encountered in the introduction of the balloon into the uterine cavity it is strongly suggestive that the syndrome under discussion is not present. After the bag is inserted, a measured amount of radiopaque substance (3 to 4 c.c.) is introduced. The speculum is removed and the first x-ray taken. Traction is then placed on the balloon and another picture taken. This will give a good outline of the cervicouterine angle and the area of the internal os. Small amounts of Urokon are then removed successively from the balloon and, with traction on the cannula, x-rays are taken serially to demonstrate the contour of the entire cervical canal. Three to four x-rays are necessary for this aspect of the test (Figs. 2 and 3).

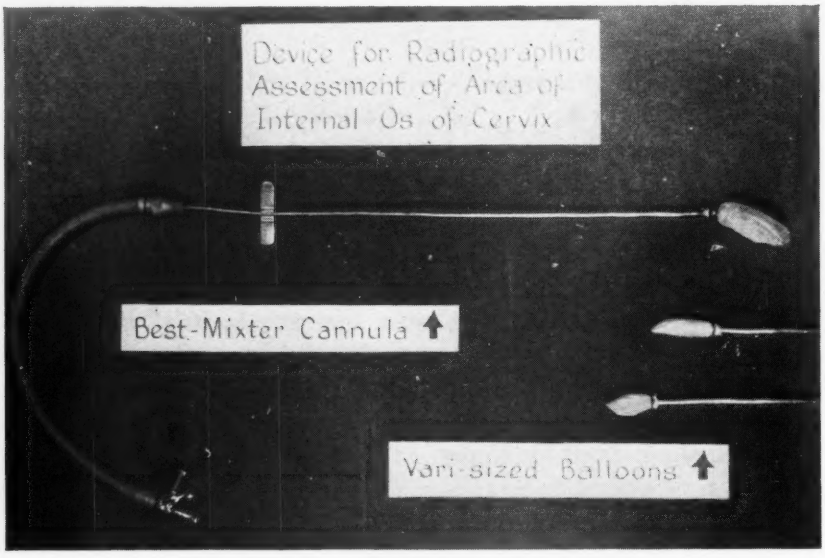

Fig. 1.

2. Lipiodol Technique.—Following the withdrawal of the balloon a Rubin cannula is inserted into the cervical canal. Four to 5 c.c. of Lipiodol are instilled and an x-ray taken. The next x-ray should be taken simultaneously with the withdrawal of the cannula, leaving the tenaculum in place to designate the position of the external os.

With the cannula in place in a normal cervix, the cannula tip completely fills the internal os and there is no flow of the Lipiodol solution into the canal around the cannula tip. In the presence of anatomic defects of the area of

the internal os the converse is true. Since the caliber of the area of the internal os is increased, the metal tip of the Rubin cannula is too small to provide an effective plug and allows the Lipiodol solution to flow downward around it. When the cannula is removed, allowing the Lipiodol to flow out of the uterus, the radiograph will demonstrate whether there is any significant widening of the internal os and cervical canal and also whether the normal sharp demarcation has been disturbed at the uterocervical junction. In a normal cervix the typical radiograph is as demonstrated in Fig. 4. Fig. 5 demonstrates the radiographic picture obtained where an incompetence of the area of the internal os is present. A typical control, a grand multipara, shows no abnormality of the cervix (Fig. 6).

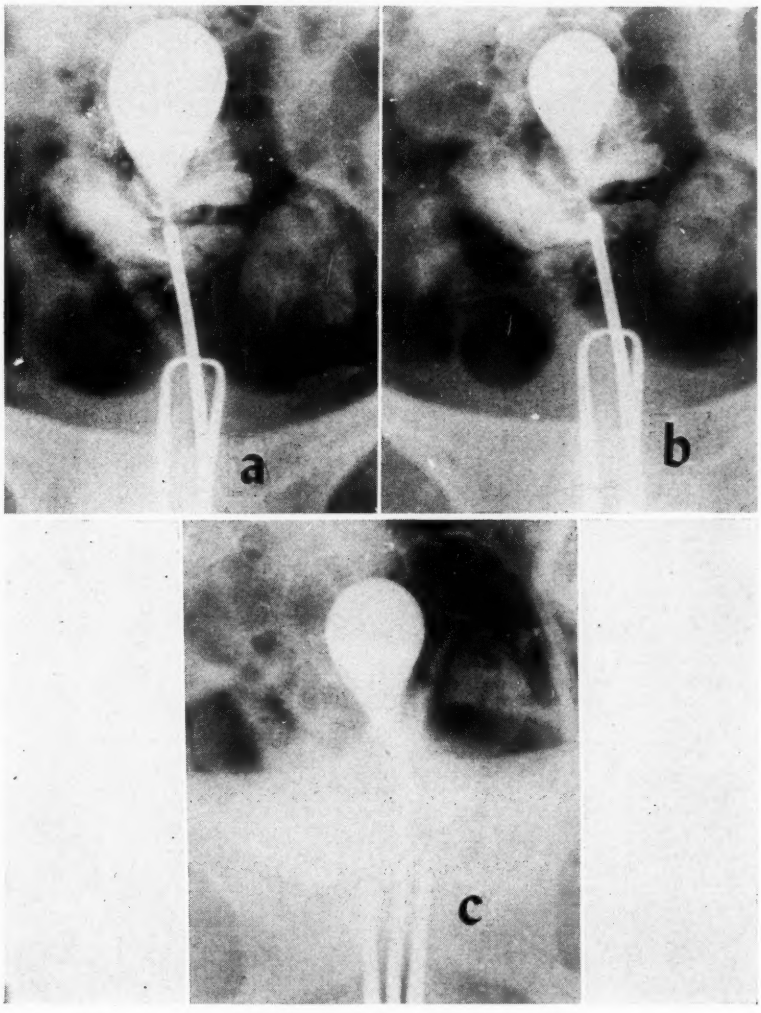

Fig. 2.—Shows the balloon technique in a normal case.

Clinically, in cases of an incompetent area of the internal os, it has been our observation that a uterine sound can be passed with ease through the cervical canal into the uterus without meeting any resistance, and frequently the cervical canal may accommodate a Hegar dilator of 6 to 8 mm. in diameter.

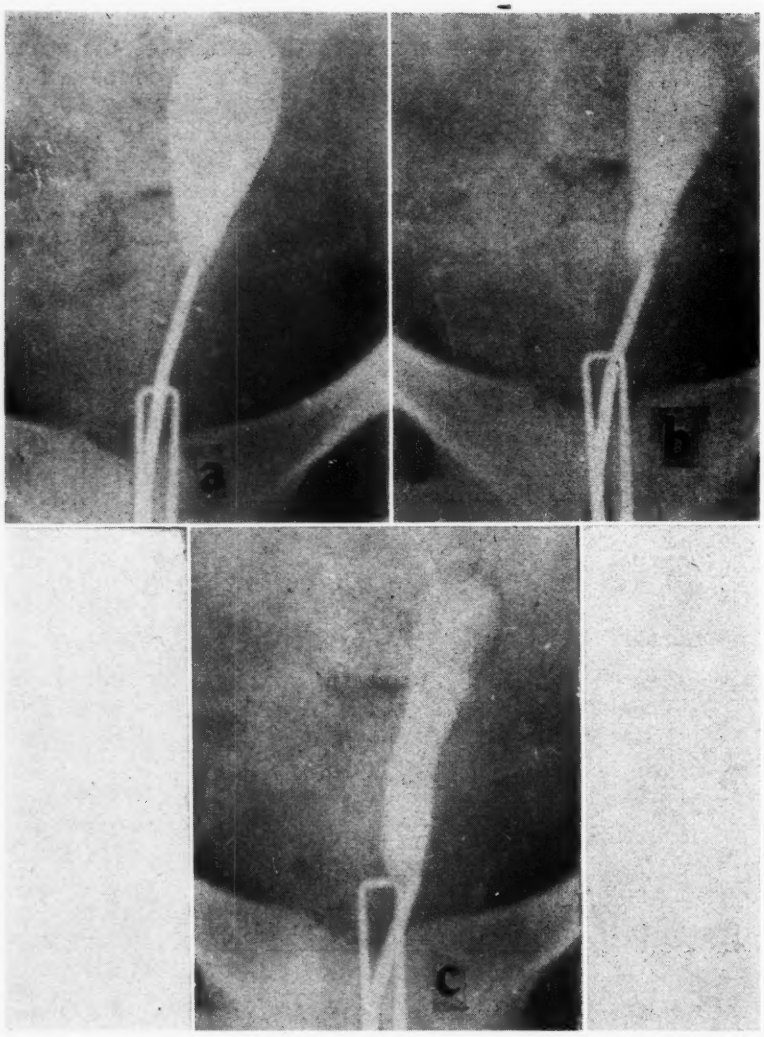

Fig. 3.—Shows balloon technique in an abnormal case, a dilated internal os.

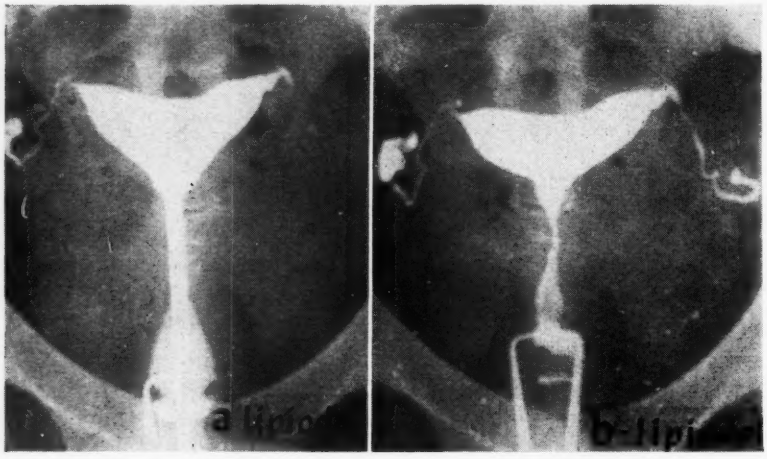

Fig. 4.—Demonstrating a normal internal os by Lipiodol injection.

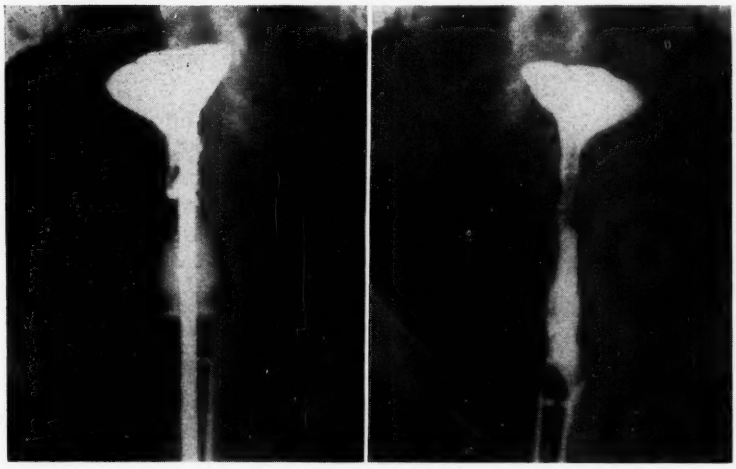

Fig. 5.—Shows the radiographic picture with the use of Lipiodol in an incompetent internal os.

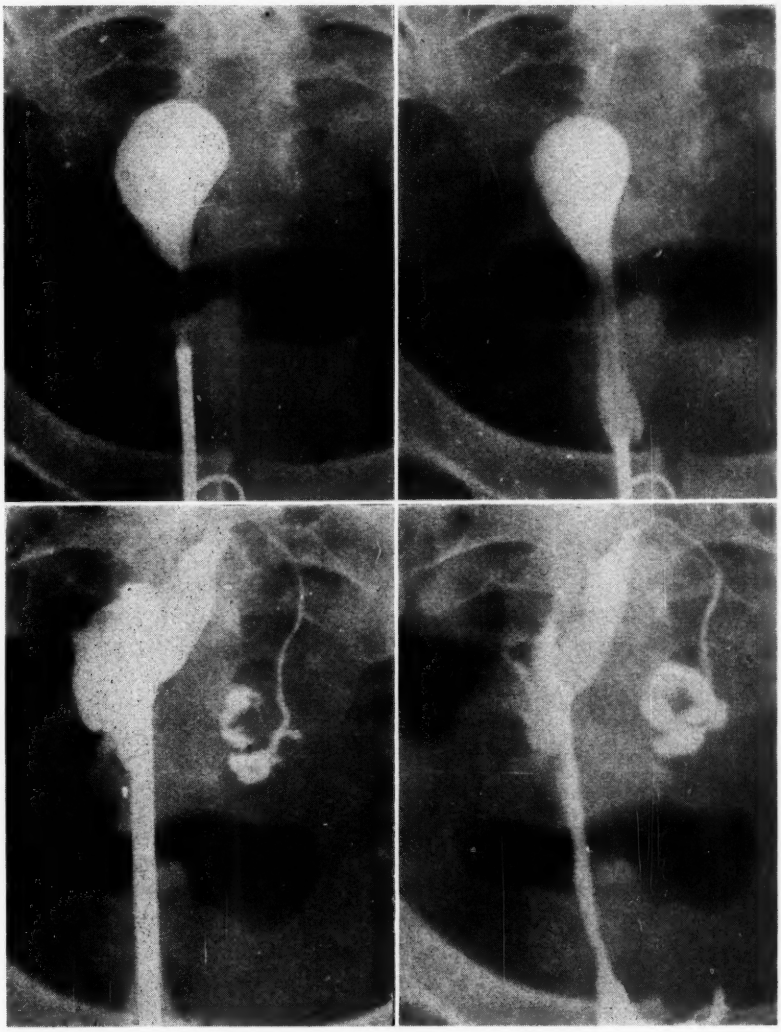

Fig. 6.—Shows a competent internal os by both balloon and radiographic technique in the uterus of a multipara.

Case Histories

To date we have investigated radiographically over 50 cases in the development of the diagnostic technique. We are using the following selected cases as representative of a radiographic method of demonstrating incompetence of the area of the internal os. Some of these were surgically corrected and have carried babies beyond viability. In others, although the lesion was demonstrated and surgical correction undertaken, a recurrence of second-trimester abortion occurred, apparently because of unsuccessful repair. Finally, cases are included in which although second-trimester abortions occurred, the lesion could not be demonstrated and other etiological factors were present.

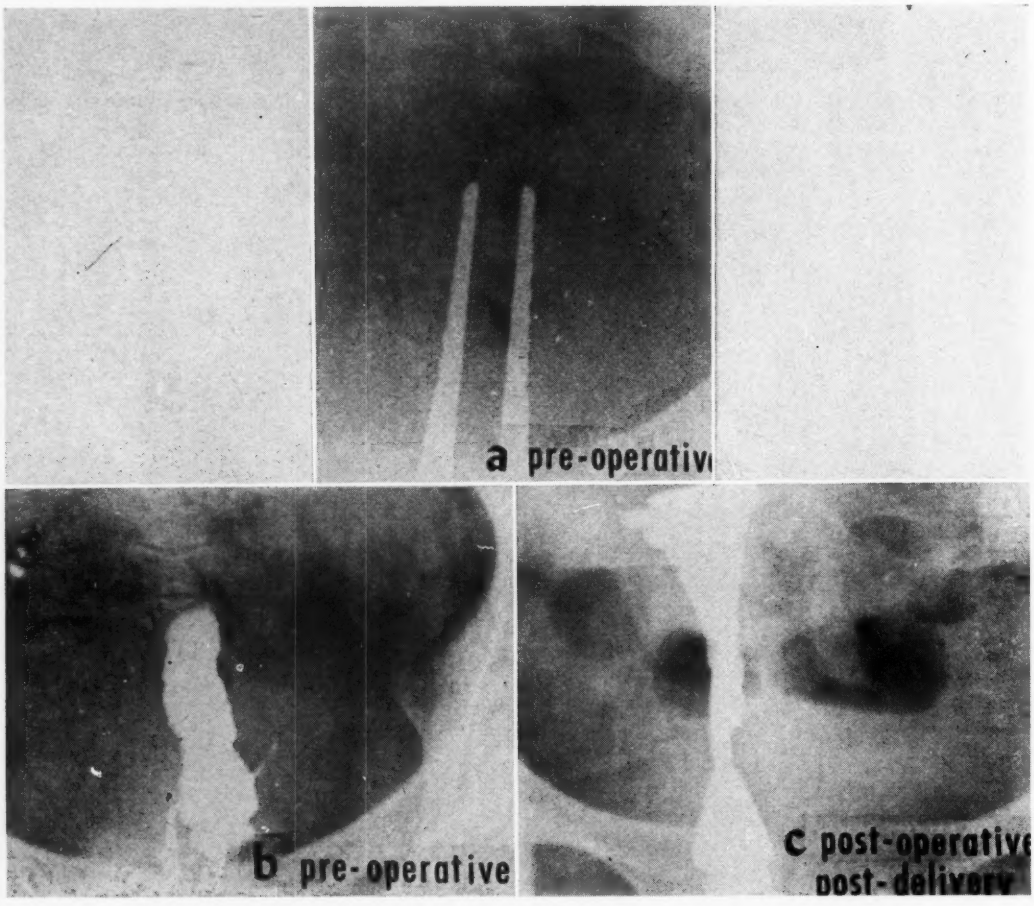

Fig. 7 (Case 1).—Shows the incompetent internal os before operation by Goodell dilator and by radiographic technique and result after repair.

CASE 1.—Mrs. J. D., aged 27 years, had a negative surgical, medical, and menstrual history. In 1941 the patient had had an induced abortion at 6 to 8 weeks. Voluntary sterility followed this until 1948 and 1949 at which time the patient had 3 abortions varying from 12 to 24 weeks. Prior to the last abortion, the basal metabolic rate and pregnandiol determinations were normal. The patient received stilbestrol according to the Smith technique. In October, 1949, a diagnosis of incompetent cervix was confirmed radiographically, and surgical repair was undertaken in 1950. The patient was delivered in February, 1951, approximately 2½ weeks prior to term. No special precautions or special restrictions were

placed upon the patient. She came to the office at regular visits. No hormonal agents were used. Postoperative x-rays demonstrated the successful reduction of the caliber of the cervical canal and postdelivery x-rays showed no apparent damage from delivery through the natural passage. The patient is again 8 months pregnant and no precautions are being taken (Fig. 7).

CASE 2.—Mrs. P. C., aged 31 years, had a negative medical, surgical, and menstrual history. She delivered full-term infants in 1937 and 1941. Between 1947 and 1950 the patient had 5 spontaneous abortions occurring between the twelfth and twenty-fourth weeks of gestation. Prior to the fifth abortion, basal metabolic tests and repeated pregnandiol determinations were all within normal range. The patient was Rh negative with an Rh-positive husband. Repeated saline and blocking antibody determinations were negative. A diagnosis of incompetent cervix was confirmed radiographically in 1950 and surgical repair was undertaken. This patient was delivered in January, 1951, of a viable fetus approximately 3 weeks prior to term.

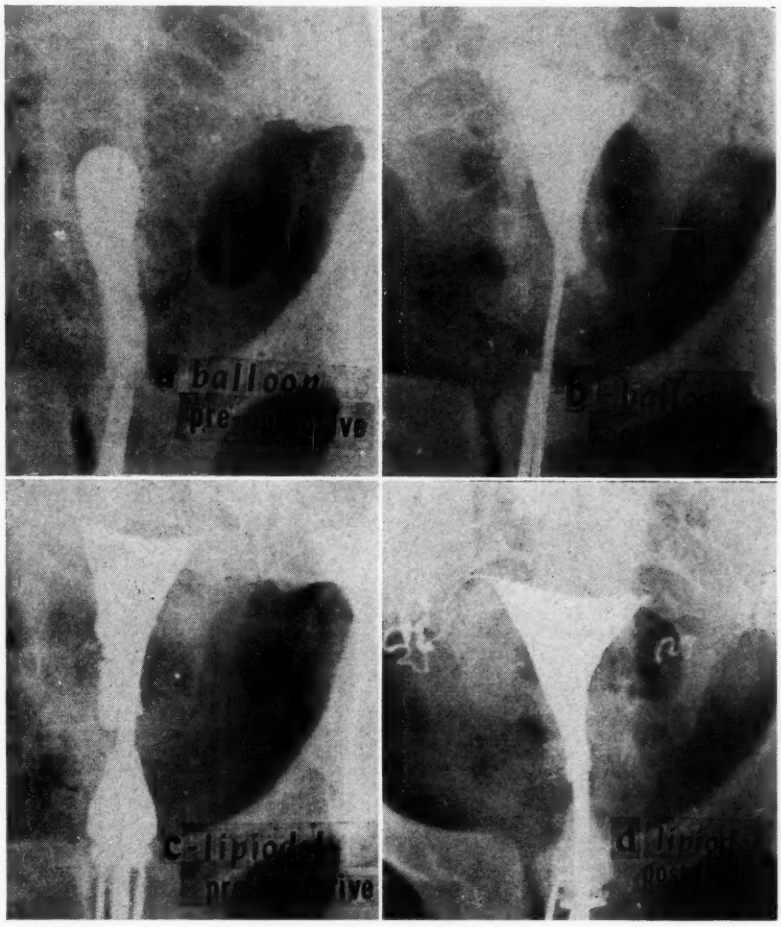

Fig. 8 (Case 3).—Shows the incompetent internal os by balloon and Lipiodol technique before and after repair.

CASE 3.—Mrs. M. C. was aged 26 years, with a past history as initially obtained entirely negative. Her general physical condition was excellent. Between July, 1950, and January, 1951, the patient had 2 abortions occurring at between 15 and 25 weeks of pregnancy. At this time the case history was reviewed and the patient questiond further with ascertainment of the following facts:

In Germany at the age of 16 the patient visited a gynecologist because of intense dysmenorrhea. In his office the gynecologist subjected this patient to a vigorous cervical dilatation as evidenced by the excruciating pain which the patient reports. Because of this history of surgical trauma, radiographic studies were carried out and a diagnosis of incompetent cervix was confirmed. Surgical correction was undertaken 5 months following the last abortion and follow-up x-rays were obtained 2 months after surgical correction. However, in a subsequent pregnancy, the patient aborted at approximately 22 weeks. Exploration of the cervical canal at the time of the abortion revealed a marked thinning of the cervix in its anterior aspect as evidence of a recurrence of the defect (Fig. 8).

CASE 4.—Mrs. L., aged 33 years, was delivered in early 1948 by a difficult midforceps operation after Dührssen's incisions. This confinement was followed in late 1948 and in 1949 by 2 spontaneous abortions between the fourteenth and eighteenth weeks of pregnancy. In December, 1949, an incompetent cervix was demonstrated and surgically corrected, with the use of tantalum wire suture for the cervical reconstruction. In January of 1952 the patient was delivered of a full-term infant by elective cesarean section after an uneventful pregnancy.

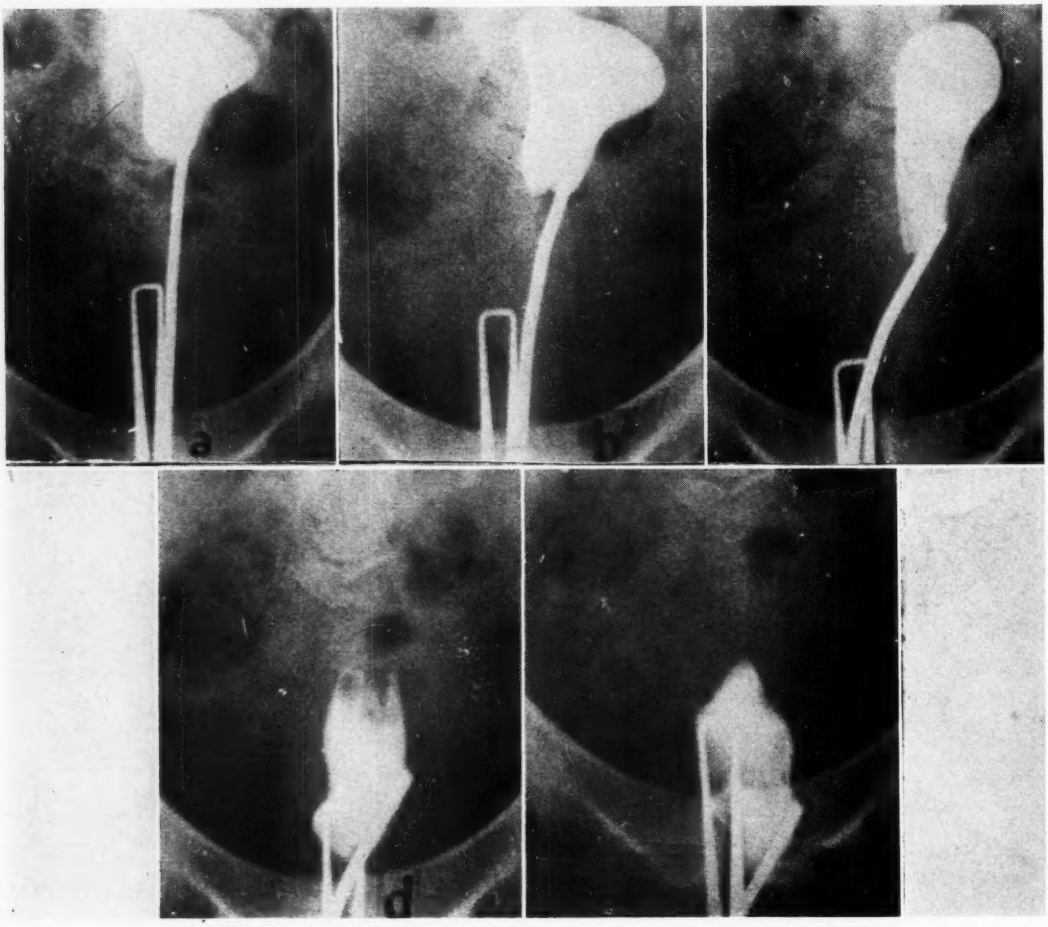

Fig. 9 (Case 5).—Shows the incompetent internal os by balloon technique.

CASE 5.—Mrs. N., aged 27 years, had a negative medical, surgical, and menstrual history. No history of trauma to the uterine cervix was obtained. Between 1948 and 1952, this patient

had three abortions between the sixteenth and twenty-fifth weeks of gestation. A diagnosis of incompetent cervix was made radiographically in October, 1952, and the surgical correction was undertaken in December, 1952 (Fig. 9).

Considerations of Surgical Repair

Initial efforts at surgical repair of this condition were first done by A. Lash as early as 1941. In the development of the surgical attack, the repair has become progressively more extensive. The technique first used was pleating of the thinned-out portion of the cervix at the level of the internal os where the defect was noted, immediately following the abortion. To accomplish this a transverse incision was made in the anterior vaginal wall and the bladder elevated to the peritoneal reflection. Multiple interrupted catgut sutures were placed in the anterior wall of the cervix, overlapping the area of the defect.

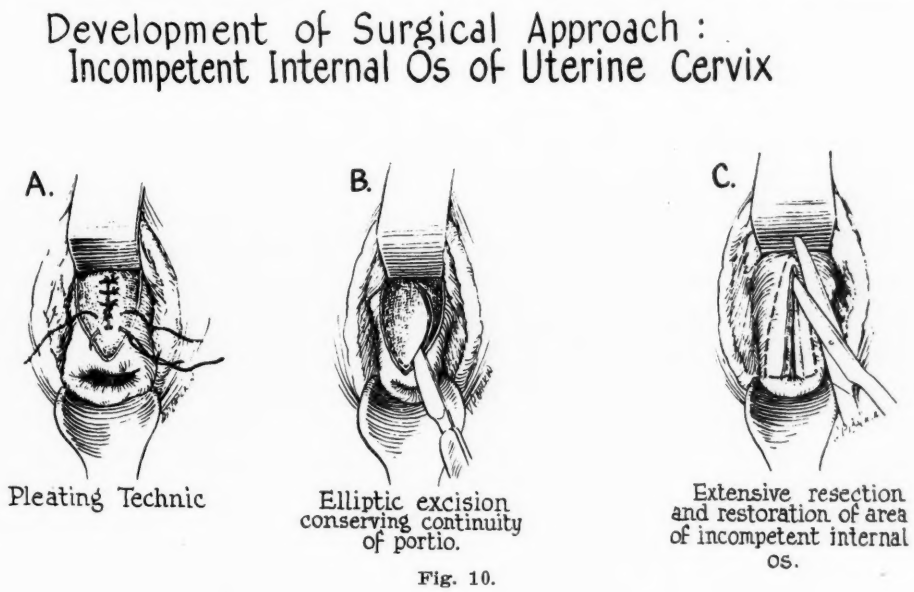
Development of Surgical Approach :
Incompetent Internal Os of Uterine Cervix
A.
Pleating Technic
B.
Elliptic excision conserving continuity of portio.
C.
Extensive resection and restoration of area of incompetent internal os.

Fig. 10.

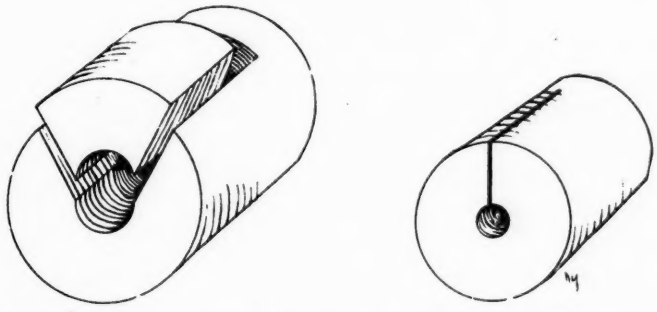

Fig. 11.—Diagram of principle of surgical correction of area of internal os. One-half of the circumference of the cervical canal must be surgically removed to reduce the diameter of the cervical canal one-half; i.e., the diameter will vary directly as the circumference.

The next type of repair included the removal of an elliptical segment of the cervical tissue without destroying the continuity of the external os, after which reconstruction of the cervical canal was accomplished. More recently, a vaginal-hysterotomy-type incision was used. If a localized area of thin and

traumatized cervix is identifiable a segment of cervical tissue approximately 2 cm. wide in this area is resected. If such an area cannot be definitely identified, an area of 2 cm. wide and 3 to 4 cm. long is removed from the anterior wall of the cervix up to and including the level of the cervicouterine junction (Fig. 10). In some cases tantalum wire has been used in place of catgut suture. If the area of repair was noted to be avascular it was felt that the tantalum wire might afford a more secure repair.

Repairs have been done electively on the nonpregnant well-involuted uterus or carried out immediately following abortion. To accomplish adequate narrowing of the area of the internal os a wide segment of tissue must be resected. As the diagram (Fig. 11) indicates, to reduce the diameter of the cervical canal to one-half its original size, half of its circumference must be surgically removed.

Postoperatively, all our cases have been essentially uncomplicated, requiring a 4 to 5 day hospitalization. Antibiotics have been used routinely in an effort to insure primary healing. The follow-up radiographic studies are usually done approximately 2 months postoperatively.

Discussion

In virtually all of our cases there is an antecedent history of trauma to the cervix. This is somewhat at variance with the observation of Palmer, who demonstrated with his manometric hysterographic techniques a widening of the isthmus which resulted either from previous childbearing or the presence of congenital uterine anomalies. The types of trauma observed by us have been: (1) criminal abortion, (2) overzealous cervical dilatation, (3) traumatic delivery at term, (4) section of the cervix at cesarean section, (5) true precipitate labor, or (6) Dührssen's incisions. As a corollary to these findings is Fisher's[4] observation that disturbance of the cervical complex by high amputation causes a marked increase in abortion and premature labor.

In October of 1950 Palmer[5] further discussed his cases referred to above. He considered the gaping of the cervical isthmus to be established if an 8 mm. Hegar dilator traversed the internal os without resistance, in the nonpregnant uterus. He postulated that the etiological factors were traumatic, congenital, or neurofunctional. He maintained, if an abortion occurred in this type of case after rest, sedation, and hormonal therapy, surgical correction of the isthmus and cervix was indicated. Our observations confirm the facts as described, except that we feel that the traumatic etiology is by far the most important. Congenital and neurofunctional types of incompetence of the internal os area may exist and may account for those of our cases in which the history of abortion is typical, the radiographic picture demonstrated, but no history of trauma can be elicited. We emphasize the importance of demonstrating the lesion under discussion, prior to any surgical attack upon the cervix. There are other etiological factors in second-trimester abortions and radiographic investigation of these cases has demonstrated a competent internal os. In some cases where no etiological factors have been found, we are at a loss to explain these abortions, but at this time we feel that there should be no surgical attack.

Where the lesion under discussion has been demonstrated no measure such as the use of hormonal drugs, bed rest, or sedation has proved adequate

for the conservation of pregnancy. Surgical correction of an existent incompetent internal os is apparently the treatment of choice. As the surgical technique has been developed over the years, we find ourselves doing a progressively more extensive and adequate repair. The need for this is inferred by the observation that in several instances, although mothers have carried babies to viability, they have delivered several weeks early. We have at least 2 cases now in which more than one baby has been delivered through the birth canal following the operative procedure, which implies that, once the correction has been accomplished, subsequent childbearing does not destroy the effectiveness of the successful repair. In the instance of a term pregnancy where tantalum wire was used as a suture material, cesarean section was elected. The relative merits of the various suture materials remain under investigation. Fertility is unimpaired by surgical correction of the incompetent internal os. In every instance here reported, except for the one recent case mentioned, pregnancy has followed within 6 to 9 months of the surgical procedure. The surgical reconstruction of the area of the incompetent internal os may be accomplished either at the time of the abortion or 2 to 3 months later. We have carried out the repair under both conditions and it has proved effective. The relative merits cannot as yet be evaluated adequately until we have acquired more extensive experience.

On the basis of our clinical, radiographic, and surgical experiences with patients of the type reported, it appears that the ability of the uterus to contain and carry a pregnancy is a function in part of the competence of the area of the internal os, including the cervicouterine angle, the anatomic internal os, and the cervical structure immediately subjacent. Conversely, distortion and widening of this region of the internal os, whether from anomalies or trauma, will interfere with the continuation of pregnancy. If the anomaly or injury is of a high order, abortion in the second trimester will result. It is tempting to speculate on the possibility that distortion of a lesser degree may be etiological in some instances of premature labor.

Summary and Conclusions

This presentation consists of a relatively small number of selected representative cases of incompetence of the area of the internal cervical os. The following clinical and laboratory picture has evolved: The patient will usually have two or more second-trimester abortions. In the majority of cases, history will reveal some traumatic factor to the uterine cervix. Physical examination will reveal no significant general physical abnormality. Radiographic studies as described will reveal the characteristic changes in the area of the internal os. When such a diagnosis is established, surgical correction of this condition can be accomplished by several techniques and affords a promising method to restore the childbearing function of the affected woman. Unless such an anatomic lesion can be demonstrated we feel that all other possible causes for second-trimester abortion should be investigated and that sur-

gical attack is not indicated. We present this series in the hope that others will consider a similar program of study which will afford refinements in techniques of diagnosis and treatment.

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Discussion

DR. D. N. DANFORTH.—The present paper is an extension of the work which was presented before this society in 1948. It differs from this preliminary presentation in several important respects. First, the authors present clear-cut, objective evidence of an actual defect in the lower pole of the uterus. Second, five dramatically illustrative cases are outlined. And, third, an effective surgical technique for the correction of this defect is presented.

In the discussion of the original presentation, exception was taken to the hypothesis that incompetency of the internal os, per se, was responsible for late abortion, and that surgical tightening of this area alone could prevent this accident. In 1946, also before this society, evidence was presented to demonstrate that the internal os of the nonpregnant uterus vanishes in the gravid uterus at about the twelfth week of gestation as the isthmic segment "unfolds" or dilates to receive the growing conceptus. Evidence was also presented to show that after 12 weeks' gestation, which is the critical period to which the present paper refers, it is the cervix itself, by virtue of its fibrous structure, which constitutes the barrier confining the conceptus to the uterine cavity. It was also suggested that one might logically expect late abortion to occur if the integrity of the cervix were disrupted, as by high laceration or previous amputation.

My objection, therefore, is one of terminology. I believe that it is not the internal os which is weakened, but rather the cervix itself by virtue of a defect in its upper portion. The terms used in describing their cases, and the nature of the corrective operation they now use, suggest that the authors are fundamentally in agreement.

In conclusion, may I say that I believe an excellent case had been made for the role of cervical incompetency as an important factor in certain cases of late abortion. The authors have shown further that such incompetence may result from forcible dilatation of the cervix, or from physiologic dilatation in labor. They have also presented a reasonable means of diagnosing this defect, and an effective method for its repair. I consider this an important contribution, and wish to congratulate the authors.

SEPARATION OF THE SYMPHYSIS PUBIS*

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(From the New York Lying-In Hospital)

THE study of the pelvic ring dates back to Hippocrates, whose doctrine held that the pelvis (meaning symphysis) separated at the time of the first labor and remained so thereafter.

Andreas Vesalius in 1543 first advanced the concept we hold today, that the pelvis is a comparatively unyielding bony ring. Ambrose Paré, on the other hand, believed that the pelvis yielded. In support of this latter theory Le Gallais in 1812 demonstrated that the capacity of the guinea pig pelvis increased twofold to pass the head. Duncan in 1868 noted separation of the pelvis in the cow at term, manifested by the "sinking of the rump." The dog pelvis, on the other hand, is known to undergo early ankylosis.

The clinical significance of the complication of separation of the symphysis in the human being has been regarded as of serious import. So great an authority as DeLee once looked upon the complication as associated with a mortality rate of approximately 35 per cent, partially due to the accompanying high incidence of sepsis. James states: "Rupture of the pelvic girdle during labor is a serious accident which carries with it a high mortality. If recovery follows, it is likely to be tedious, and often some permanent disability remains." Other authors have universally held the same outlook.

Because of this viewpoint, it seemed worth while to investigate a recent series of separations. As such, those diagnosed and treated at the New York Lying-In Hospital from 1932 through September, 1952, were reviewed, and the results herein reported in comparison with those given in the previous literature.

The symphysis is described by Piersol as a typical "half joint," the fibrocartilage coating the opposed surfaces being very dense, and the central cavity or cleft being small, and lying nearer the back than the front. In the nonpregnant state, the normal breadth of the soft parts rarely exceeds 5 mm. The cartilages are ensheathed in fibers and are inseparable, those above and behind being of little consequence. The anterior or subpubic fibers are much more dense and form the main transverse bands (Fig. 1).

Spalteholtz points out that a fibrocartilaginous disc lies between the hyaline-cartilage-covered bones. This projects as a narrow ridge posteriorly, while in front it broadens and is intimately connected with the deeper fibers of the anterior ligament. The deeper fibers of the strong inferior or arcuate ligament are also intimately connected with the fibrocartilaginous disc. The origin of the joint space or fissure is as yet obscure. Since it is not found in

*Read at a meeting of the New York Obstetrical Society, Feb. 10, 1953.

the newborn but has appeared by the time bone growth has ceased (about age 24-25), it is thought to be due to vascular degeneration secondary to weight-bearing and the continual trauma of walking.

Mechanically the symphysis serves to anchor the ends of the two weight-bearing arches of the pelvis—the femorosacral and ischiosacral arches. Under normal conditions it has been found to be exceedingly resistant to separation. As early as 1864 Poulett noted that a 170 to 280 kg. direct pull was necessary to separate the symphysis on the autopsy specimen. Widely quoted is DeLee's statement in which he estimates the force required to rupture the pelvic girdle as between 400 and 2,600 pounds. He feels further that this extraordinary amount of force required to disrupt the symphysis does not occur in labor or delivery. Rather, there is some predisposing factor or inherent weakness such as caries, rachitis, trauma during pregnancy, or congenital weakness, which contributes to the separation. Kehrer also believes that a pathological exaggeration of the softening process predisposes to rupture.

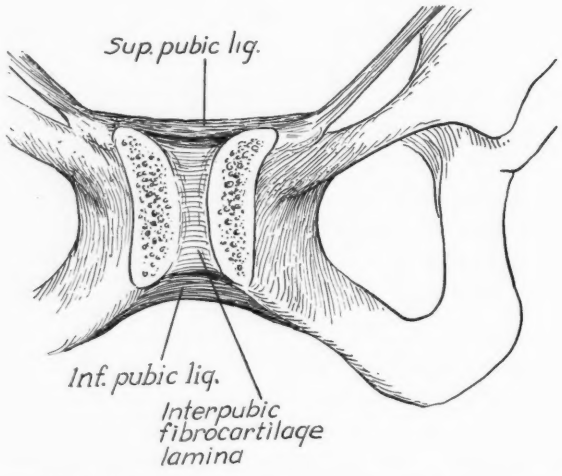

Fig. 1.—The main supporting ligaments of the symphysis with a schematic representation of the joint space.

The actual pathology of the separation is a rupture of the previously mentioned pubic ligaments. Only exceptionally, however, is there a complete loss of the bridge, with usually some fibers or cartilage remaining. Hemorrhage into the cavity thus created, and edema are the usual sequelae. However, severe hematomas are rare, although a fatal one has been reported by Holzbach. Infection usually occurs if there is a connecting vaginal laceration, and severe suppurative arthritis of the joint with osteomyelitis is infrequently reported. In the past this has been considered to be a most serious added complication.

As a rule the hinging effect on the sacroiliac joint is thought not to be harmful unless the separation is 4.0 cm. or greater. Reis, Baer, Arens, and Stewart thus report sacroiliac involvement in 22 of 67 cases. Sacroiliac symptoms rather than actual damage to the ligaments or joint are the rule.

The picture has been described in the parous woman as one of lack of ligamentous structure, with joint formation. Extensive fatty degeneration and calcium deposits are said to occur in the joint during pregnancy. Heyman and Lundqvist state that arthritic changes in the pubis are common in high multiparas.

The effect of such a separation on the capacity of the pelvis is interesting. Hebeosteotomy or symphysiotomy has been and is still being used for vaginal delivery in the minor disproportions. In spite of its success in achieving greater pelvic capacity, however, the procedure is obsolete in this country because of the high incidence of delay or lack of union thereafter, often resulting in a false joint with motion, demonstrable in subsequent pregnancies. Bertin, by x-ray studies, concluded that maximum physiological widening of the symphysis did result in an ultimately more favorable course of labor in the primipara, even though there might be no demonstrable widening of the superior strait. Döderlein (quoted by Boorstein) calculates that a gap of 6.7 cm. increased the capacity of the superior strait by 50 per cent. Boorstein states that even a gaping of the symphysis of from 3 to 6 mm. increases the capacity of the superior strait 12 to 13 mm.

X-ray studies by numerous observers call attention to the separation of the symphysis of a minor degree after which is symptom free. Others have noted an antepartum widening of the symphysis with the greatest increase noted in the fifth to seventh month. Müller reports on 100 patients x-rayed before labor and one day post partum, finding slight separation "normal" and decided that separations are quite frequent.

In this study, therefore, true separations (or rupture of the symphysis) are considered to be those associated with clinical symptoms, rather than with x-ray findings alone. Even 3 to 5 cm. separations cannot be considered as true ruptures in the absence of clinical symptoms. Generally, however, separations of 1.0 cm. or over are considered to be symptom producing.

The reported incidence varies markedly. This is in part due to the varying criteria used for diagnosis, as well as the inclusion of antepartum separations, traumatic or otherwise. Reis, Baer, Arens, and Stewart reported 62 cases of rupture (complicating spontaneous delivery) in the literature up to 1932. They state that ruptures are five times as likely to occur in operative as in spontaneous deliveries, but consider that because of the increasing use of cesarean section this may no longer hold true. Boland, on the other hand, reports an incidence of 1:685 at the Boston Lying-in Hospital, stating that the condition is much more frequent than was realized. His figure includes both spontaneous and operative deliveries.

In our own series, covering 20 years, there were 30 cases which could be considered true ruptures in about 65,000 deliveries, or an incidence of about 1:2,200 (including operative, spontaneous, and antepartum separations). Of these 30, 6 were in primigravidas. The remaining 24 patients had delivered from 1 to 9 full-term infants previously, 17 of the 24 being para i. This suggests that the multipara is far more susceptible to separation. Seventeen

cases occurred following spontaneous deliveries, nine after operative deliveries, and four in the antepartum period.

The actual diagnosis of a classical rupture presents no problem. Almost without exception the prime symptom is pain in the symphysial region. X-ray is rarely necessary for diagnosis. The woman herself during delivery may state that "something has burst," or the accoucheur may hear a loud crack, following which a difficult delivery may become easy.

Any movement causing motion of the symphysis will cause pain. This may be sharply localized but often may be referred to or also involve the sacroiliac joints because of the hingelike effect. If these patients are able to walk, because of external rotation of the acetabula and trochanters a typical "waddling gait" results, or a dragging, shuffling type of walk, depending on the severity of the separation.

Various minor symptoms may occur—inability to turn in bed, or urinary difficulties if the urethra or bladder is involved. A "pseudoparalysis" or involuntary splinting of the lower extremities for protection against the pain of motion may occur. Sciatic-type pain occasionally accompanies sacroiliac involvement.

Diagnosis is made on these symptoms plus certain classical physical findings:

1. Tenderness (possibly with edema or ecchymosis) over the symphysis and/or sacroiliac regions.
2. A gaping or defect which may be palpable over the symphysis.
3. Motion of the symphysis on pressure, voluntary movement, or on walking, which usually is associated with severe pain. Crepitus may be elicited along with the false motion.
4. Eversion of lower extremities with external rotation of the acetabula.
5. X-ray, probably the least important aid in diagnosis. This may reveal anything from mild to marked displacement. The wider, more serious separations are usually easily palpable and have such marked symptoms that x-ray is merely an added confirmation.

Of further aid is the preceding history, whether of antepartum trauma, or the type and circumstances of anesthesia and delivery.

The mishaps causing rupture fall into several categories. Basically there are two—the expansile wedge effect (Fig. 2) and the tractile "pull" effect, or, rarely, a combination. Of the two it is probable that separations due to expansile forces are more common.

A driving rapid labor probably accounts for the majority of symphysial ruptures seen in spontaneous deliveries. This occurs with greater frequency in the multipara (3 to 1 in the present series) where some previous relaxation of the ligaments has occurred, and precipitate delivery with a larger infant is more likely.

Of 30 cases reported herein, 3 could definitely be said to have followed rapid labor with a large infant; 5, or 17 per cent, followed difficult forceps

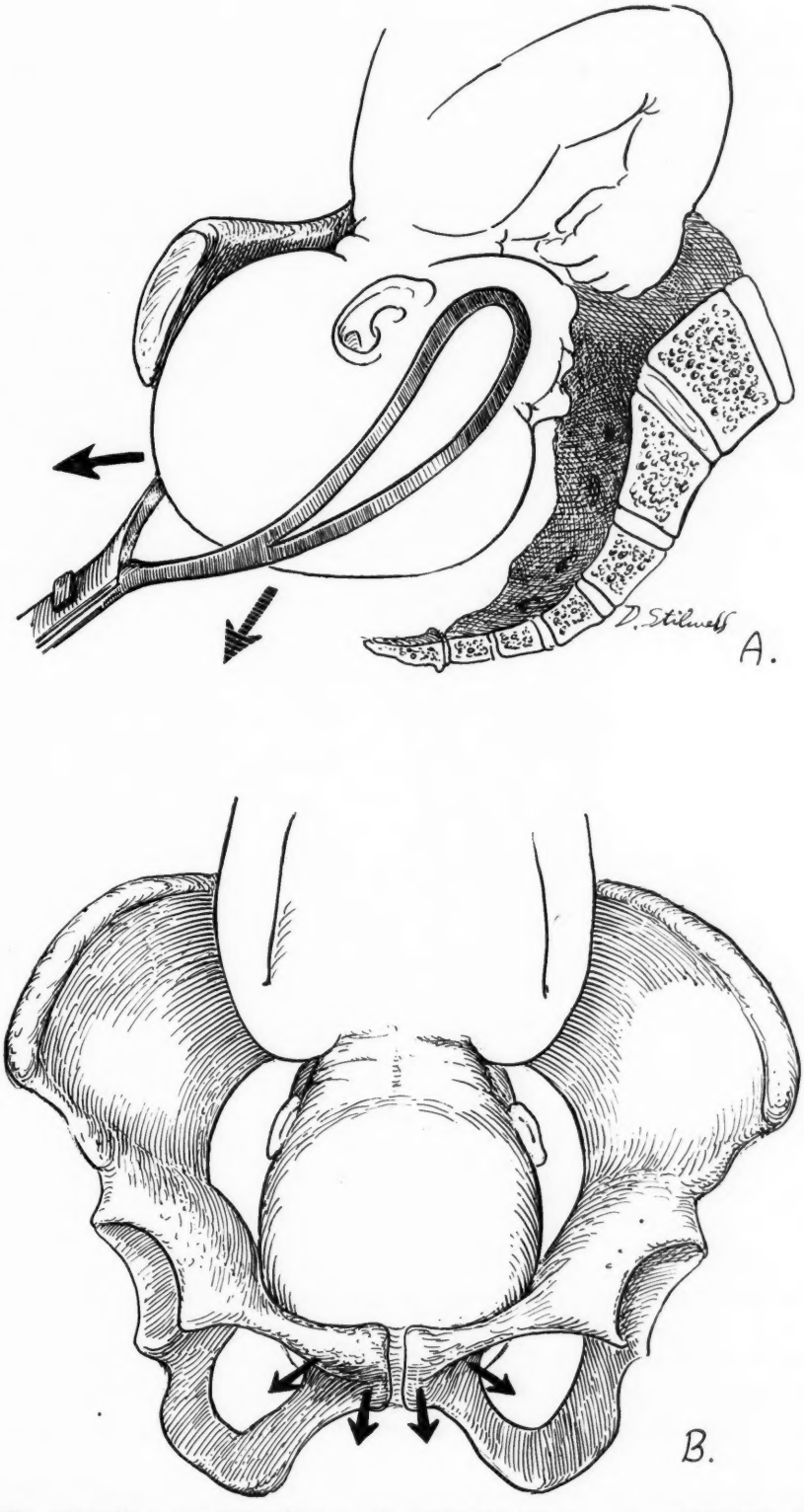

Fig. 2.—The expansile or "wedge" effect on the symphysis due to: (a) misdirection of tractile force and (b) a relative disproportion (large infant or small pelvis).

operations, including one high and several difficult midforceps rotations. With misdirection of traction against the pubic arch rather than in the pelvic axis, a great deal of expansile pressure would be brought against the posterior surface of the symphysis (Fig. 2). In like manner, difficult rotations or rapid forcible forceps deliveries could cause the same result.

Closely associated is the problem of the relative disproportions. Whether due to a large infant or a contracted pelvis (justo minor, funnel, or narrow transverse), the tendency is toward the expansile effect. A relative disproportion of any degree associated with rapid labor or forceps delivery where molding has not been accomplished will increase the likelihood of separation. However, only 1 of 30 pelves was classified clinically as contracted.

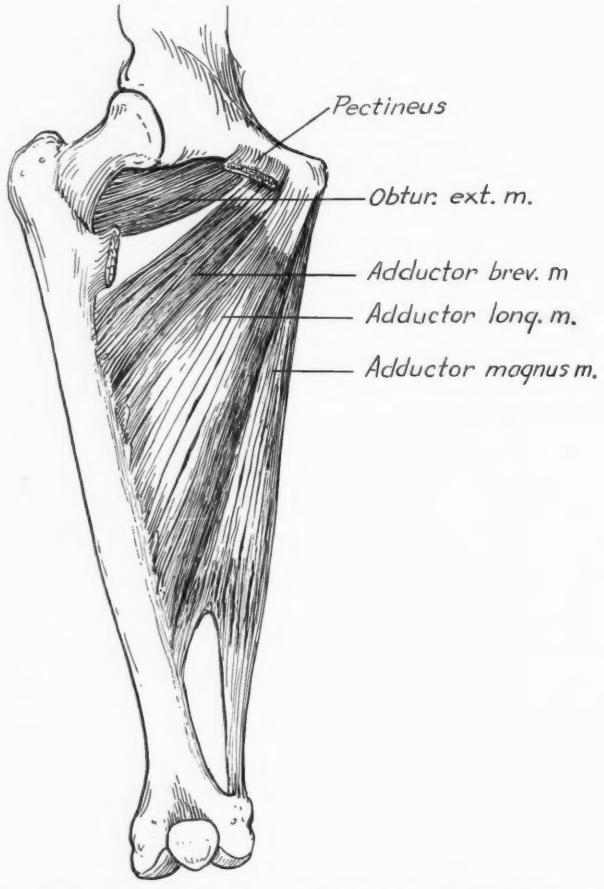

Fig. 3.—The adductor muscle group anchored to the pubis, responsible for strong tractile force on the symphysis in forcible abduction.

Abnormal presentations or abnormal infants such as those with hydrocephalus occasionally contribute to rupture. One face presentation, 3 sets of twins, 1 impacted shoulder in a 5,360 gram infant, and 2 breech presentations were noted in this series.

One of the less familiar but possibly very important causes is the extensive trauma caused by either forcible restraint or abduction of the thighs

during delivery (Fig. 3). This includes the injury a patient may cause herself while struggling on the delivery table with her legs in stirrups. This follows heavy analgesia or light anesthesia, which result in a noncooperative patient.

In this series 3 case histories have a notation of forcible restraint, and in 2 note is made of a loud crack followed by immediate passive abduction of the thighs. It is impossible to evaluate how many "spontaneous separations"

Fig. 4

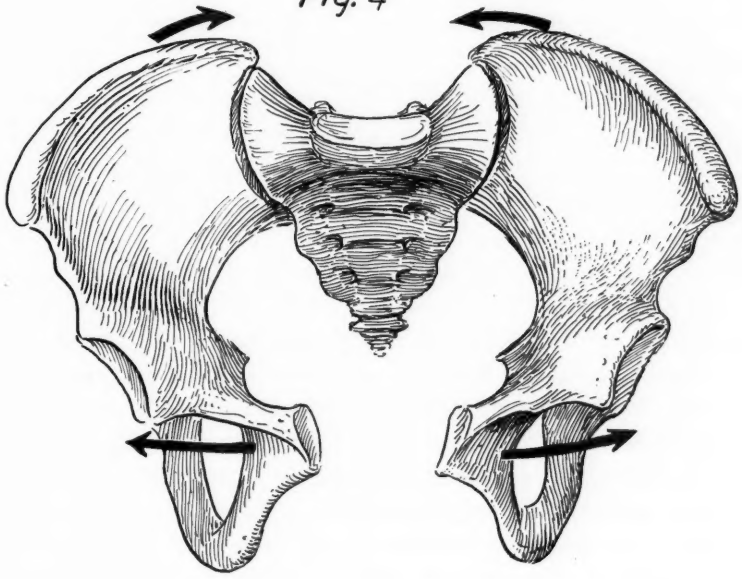

Fig. 5

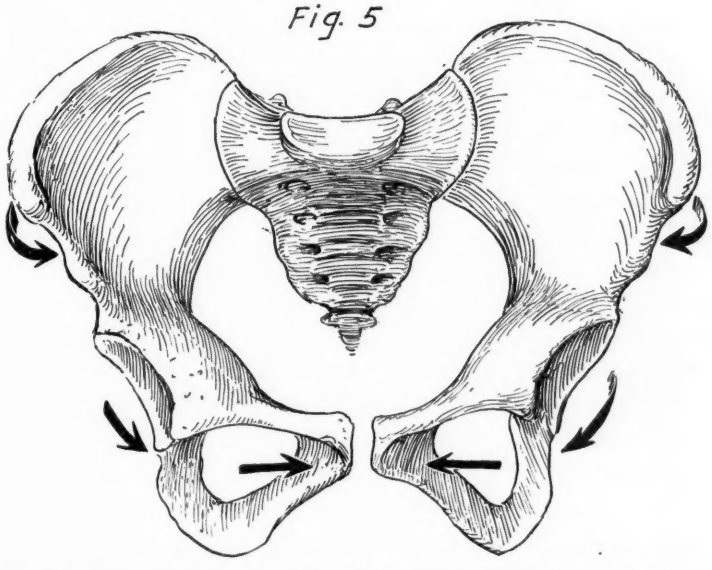

Fig. 4.—The mechanics of separation showing the hinging effect on the sacroiliac joints.
Fig. 5.—The principles of reduction by medial pressure over the iliac crests, and maintenance by circular pressure.

really result from well-meaning but forcible abduction of the thighs. This point has not been made in the past, and probably deserves more attention.

Prenatal separations also occur occasionally. Sometimes there is no history of antecedent trauma, such as a fall, automobile accident, or even exceptional physical effort like heavy lifting. Four of these series had symptoms ante partum, 3 following trauma (fall, collision) and 1 apparently without cause. It is probable that abnormal softening and weakness of the symphysial ligaments contributed.

There remain a certain few in whom no cause for the separation can be found. Pathologic softening is here highly suspect. Three of this series must be so classified.

The management of separation is at once simple in principle and difficult to execute. Obviously, the desired result is reapproximation and immobilization of the separated symphysis. In actual practice this is a problem which is trying and must be individualized. Reported treatments are varied and some seem quite bizarre.

If soft part or vesical injuries are present, immediate repair of these structures and use of an indwelling catheter will be necessary. Attention then may be turned to the means of reducing and immobilizing the separation. The most common (and probably most generally satisfactory) method of early treatment is the use of heavy complete circular adhesive strapping, applied while assistants exert medial pressure on each iliac crest and over the trochanters (Figs. 4 and 5). In this manner varying degrees of reduction can be obtained, usually with marked relief of the symptoms while the patient remains in bed. Due to the tendency of adhesive to slip, however, maximum effect of the strapping will not last over 48 hours. Consequently, its replacement with a heavy orthopedic adjustable girdle belt is advisable. This plan of treatment instituted early will suffice for most cases.

Other methods used in the individual case include: (a) the Bradford frame maintained for 2 to 4 weeks, followed by a belt; or (b) a circular plaster jacket (usually unsatisfactory); (c) "elephant sling," a canvas sling and traction; and (d) sandbagging, often an adjunct to the above procedures.

In some instances of wide or long-standing separation, conservative measures alone do not suffice. Many surgical procedures have been devised.

Allen reports an unusual procedure where reduction could not be maintained by external means or by Lane plating. Two-inch wire nails were driven into each iliac crest, protruding one-half inch. Sterile iron wire was wound across the abdomen three times, and the whole incorporated in a snug plaster jacket. He reports the patient walking in less than 8 weeks and in perfect condition 2 years later.

McNamara reported the case of a 38-year-old para vi who had been subjected to an instrumental delivery six months earlier, and who had been unable to walk since that time unless she supported herself on a chair which she pushed around in front of her. Examination revealed an 8 cm. gaping of the symphysis in which a fluctuating tumor could be palpated (bladder).

After unsuccessful trials with plaster jacket, girdles, and strapping, an open reduction with wiring through the obturator foramen was done. Single Lane plates were also applied anteriorly and posteriorly. The Lane plates had to be removed in eight weeks but satisfactory return of all function ensued. McNamara concludes that inability to walk in the postpartum period should call for an examination of the symphysis pubis.

Boland reports a low forceps delivery with a tear through the clitoris and wide separation. While the patient was still under anesthesia immediate repair of the separation was done with Kangaroo tendon. The end result was reported as satisfactory.

A recent word-of-mouth case report described a problem created by lack of union in a pubiotomy done elsewhere. It was finally treated by sacroiliac fusion. Follow-up has not yet been obtained. This suggests a new and interesting approach toward stabilization of the pelvic girdle.

Surgery is rarely indicated for separations, and probably is most effective in the long-standing cases. Lane plates are of no value and probably the best procedure is wiring of the symphysis. It seems that early reduction and immobilization by conservative means would obviate the need for surgery.

The long-term result remains difficult to evaluate. There have been no permanent disabilities in our series, and some of the cases have been followed over fifteen years. The period of disability varied from 2 days to 8 months post partum, with symptoms usually absent by the eighth week post partum. A patient with one of the most severe separations walked perfectly one year later with no symptoms, in spite of a palpable gap of 2.5 cm. and motion in the joint (the initial gap was 7.0 cm.). In most cases the duration of the symptoms varied directly with the degree of the separation. In several of the more severe separations there were symptoms for over six months, but this was the exception rather than the rule. Whether long term arthritic and degenerative changes will occur remains to be seen.

If infection occurs with pubic arthritis or osteitis pubis the course may be prolonged. One patient developed an abscess in the space of Retzius, treated by incision and drainage. However, the separation was incomplete, and recovery was not delayed.

What of the prognosis for future deliveries? Boland states that a previous separation will reseparate in subsequent deliveries. He cites a patient who took four months to regain normal walking power and was therefore sectioned electively in her second pregnancy. Three of the present series were sectioned for this reason, 1 having had 2 previous separations. On the other hand, 5 have had from 1 to 4 vaginal deliveries following a preceding separation. One of these had slight pelvic pain for two days which rapidly disappeared. Three others had no symptoms, although they delivered larger infants than caused the original separation.

This small series suggests that a repeat severe separation is unlikely, and that elective section should be performed for other obstetrical indications only. Possibly there is more "give" to the symphysis in subsequent pregnancies and tearing of the ligaments does not occur.

Case Reports

Antepartum Separation.—

CASE 1.—V. W., 26-year-old Negro para i, gravida ii, with a previous 10⅓ hour labor for a 3,120 gram infant, was admitted to the pavilion service in the thirty-fourth week of her present pregnancy. She gave a history of an automobile accident, following which severe suprapubic pain prevented walking. Examination revealed tenderness and a 1 to 2 cm. gaping of the symphysis pubis, confirmed by x-ray. After 5 days' bed rest she was allowed up progressively and home on the sixteenth hospital day. Before discharge, the senior consultant had advised readmission near term for elective cesarean section on the basis of separation. One week before the expected date of confinement she was readmitted in driving labor, with the head deep in the pelvis, and delivered a 2,900 gram infant spontaneously after an hour and 10 minutes of labor. The puerperium was complicated by complaints of symphysial pain. In spite of this, she walked well, and was discharged on the twelfth postpartum day. She has since had three spontaneous deliveries uneventfully.

Difficult Forceps, Large Infants.—

CASE 2.—A 39-year-old white para ix, gravida ix, with a history of large infants (11 to 12 pounds) had a tracheloplasty two years before the present pregnancy. A midforceps rotation from right occipitotransverse to occipitoanterior with Bailey-Williamson forceps, with delivery of a 4,680 gram infant, was done, the indications being "cervical dystocia and fetal distress." A large left sulcus tear was repaired, and the uterus explored manually after delivery, with packing afterward. A febrile puerperium followed, and the patient was not allowed to get up until the twelfth postpartum day. She complained bitterly of pain in the anterior pelvis on walking and was described as "dragging her legs along."

By x-ray a 0.7 cm. gap was noted. Tight circular adhesive was applied and maintained for 14 days, and she was allowed to go home on the thirtieth postpartum day, symptom free.

Forcible Abduction, Light Anesthesia.—

CASE 3.—L. S. was a 37-year-old white para i, gravida iv, with a clinically ample pelvis and a history of a 28-hour-labor for an 8 pound, 8 ounce infant previously. She was admitted at term in active labor, with the head well engaged, in right occipitoanterior position. After 9 hours of first stage, 37 minutes of second stage, the head was delivered spontaneously. Because of light anesthesia she then became unruly and drew her thighs together while an attempt was being made to deliver the shoulders. The assistants then began forcibly to abduct the thighs. A loud "tearing sound was heard and the legs fell apart." A 3,790 gram normal infant was then easily delivered.

Vaginal examination revealed a deep rent in the anterior vaginal wall extending from the pubic ramus to the urethral meatus. The symphysis could be palpated as separated "about 5 inches." (X-ray after strapping revealed a 3.0 cm. gap.)

The bladder was catheterized and the urine found to be clear. The lacerations were repaired, the separation reduced and strapped, and the patient placed on a Bradford frame. However, the adhesive strapping did not hold well and was repeatedly reapplied. An "elephant sling" was then used with good results. She was allowed up on the twenty-first postpartum day, and home on the forty-fifth day, wearing a heavy specially made belt brace.

Fourth months later there was no palpable separation and she walked perfectly. The only abnormality was a moderate vaginal outlet relaxation.

Summary and Conclusions

1. Separation of the symphysis pubis is a rare complication of pregnancy (1 in 2,000 cases).

2. Separation may occur either ante partum or at delivery.

3. The basic mechanism is either tractile (external) force, or expansile (internal) wedgelike force causing a rupture of the symphysial ligaments.

4. Forcible abduction of the thighs during delivery should be avoided, as it is a common cause of separation in the lightly anesthetized and resisting patient.

5. Treatment by strapping usually suffices. Operative repair is rarely indicated. Wiring is probably best if surgery is found necessary.

6. Recovery of function is usually complete, although some separation and motion of the joint may persist.

7. Subsequent vaginal delivery without recurrence of original symptoms can be anticipated. Elective cesarean section in successive pregnancies probably should be done only for purely obstetrical indications and not because of previous separation.

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Discussion

DR. DAVID N. BARROWS.—The Hospital for Special Surgery has drawn a great many patients from the Caribbean area where symphysiotomy has been the procedure of choice rather than cesarean section, and its staff is therefore more familiar with this particular condition. One patient at that hospital had a separation of about 7 or 8 cm., with the bladder protruding through the space, and a chronic osteomyelitis on both sides of the pubis due to attempted repair with wire and nails. The aftercare presents special problems in these cases because they combine an orthopedic defect with a protruding bladder. The patient I mentioned also had a complete prolapse of the uterus.

DR. WILLIAM E. STUDDIFORD.—I would like to know whether the incidence of this condition was the same at the beginning of Dr. Callahan's series of 65,000 as it was in the last third. Dr. Callahan looks to me as though he might have been rather young in the year 1936, so he might not fully comprehend the possibilities of a mortality in a patient with this complication.

Many of the patients with rupture of the symphysis, delivered prior to this date, were delivered by forceps after very long protracted labors and the cause of death was puerperal sepsis, not rupture of the symphysis.

I am pleased to hear Dr. Callahan state that the treatment of this condition is a conservative one. I can remember once seeing a patient with a separation, who had the very typical clinical picture which he has presented and was unable to walk. This patient also showed an extensive pelvic parametritis. I referred her to an orthopedist for a tight belt and he advocated wiring the symphysis. Such a procedure in the presence of parametritis seemed to me frankly dangerous. At my insistence the patient was treated with a belt and was walking perfectly normally in about six to seven weeks.

DR. R. GORDON DOUGLAS.—I would like to add just a few words concerning symphysiotomy as it is employed in the Latin American countries at this time. I think all are agreed that it is used less frequently now than in the past. It was my pleasure to hear Dr. Julio Ortiz-Perez discuss this subject 12 days ago in Havana. During the past year he had done the operation on four occasions, which represented an incidence in his own practice of approximately 1 per cent. In the words of Dr. Ortiz the best indication for this operation is in cases where the pelvis has a moderate contraction and just a little more room is needed to permit passage of the fetal head through the bony canal. It is no longer used where there is excessive pelvic contraction and marked disproportion.

According to Dr. Ortiz the technique is quite simple and the actual procedure can be accomplished in a few minutes. A catheter is first placed in the urethra and two fingers introduced in the vagina. An incision 1 cm. in length is made through the skin over the symphysis pubis and an especially designed curved knife is introduced just under the superior ligament of the symphysis which was illustrated by Dr. Callahan. The symphysiotomy incision is extended down into the inferior ligament but not through it. The vagina, of course, is not entered. Immediately following this procedure there is an expansion in the measurement of the circumference of approximately 1½ cm. If just a little additional room was needed, delivery is then usually accomplished with ease. The great advantage of the operation over cesarean section is that the size of the pelvic inlet is permanently enlarged and in second and subsequent deliveries no additional operative procedure is necessary. Dr. Ortiz demonstrated a patient, a doctor's wife, who walked without deformity before the members of the South Atlantic Association of Obstetricians and Gynecologists. She had been delivered about 2 or 3 weeks previously and she appeared to walk without pain or discomfort.

Apparently, what one aims to accomplish in a symphysiotomy is the same as what happens with a minimal to moderate separation of the symphysis. It would appear that it is quite possible for many separations of moderate degree to go unrecognized.

DR. THOMAS J. PARKS.—I am a little surprised at the seriousness of this discussion. When I saw what the subject was going to be, I thought you would show us some graphs demonstrating calcium deficiency. I can recall three patients in my own practice. Two were primiparous and one multiparous. The two primiparas were near term and called me to say that they just could not move except with a waddling gait because of pain. I gave them calcium intravenously, a tight girdle was applied, and they did all right. X-rays were essentially negative except for a slight or questionable separation of the symphysis pubis.

The multipara was tender over the pubes as the others were and she had a waddling gait. She also responded to calcium intravenously.

There was no complication, operation was never even contemplated, and these patients are well now.

It may be a coincidence, but they were all underweight.

DR. EDWARD G. WATERS.—Many of the older obstetricians will remember well the Walcher position. It utilizes a well-recognized transient mobility or weakening of one of the three major joints of the pelvis, all of which acquire varying degrees of physiologic laxity as parturition approaches. As a matter of fact, the Walcher position places the

patient in such a way as to increase artificially the diagonal conjugate and make vaginal delivery possible in a tight pelvis. I wonder whether many of these asymptomatic symphysial separations, not at all uncommon by x-ray, are not really only exaggerated forms of the physiologic. These of course are not comparable with the severe cases reported tonight.

The only two symptom-producing separations I have seen in private practice in the last ten years occurred during late pregnancy. I think we have seen only five or six true pathologic separations in about 100,000 deliveries at the Margaret Hague Maternity Hospital. Those which are of sufficient severity to be clinically recognized and demand treatment are relatively rare.

DR. CALLAHAN (Closing).—In regard to the case reports, one of the difficulties I found in reviewing the cases was to separate the ones that were clinically significant from those not significant. I went entirely upon the symptoms. The degree of separation of course is something that is hard to evaluate. An x-ray alone does not do it.

The point brought up by Dr. Barrows of osteitis pubis makes me wonder if sacroiliac fusion might be considered in the treatment of these cases.

PREGNANCY AND HEALED SUBACUTE BACTERIAL ENDOCARDITIS

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ONE of the most remarkable therapeutic advances of the present decade is the successful treatment of subacute bacterial endocarditis with penicillin. Prior to the use of antibiotics, this disease was frequently fatal. Thus it was rarely found complicating pregnancy. A review of the literature through 1941 revealed only 25 authenticated[1, 2] cases. At present, with the greatly improved prognosis, a new problem has arisen, namely, the management of pregnancy in cured patients.

To date, only scattered reports[3-11] have appeared in the literature and there is no unanimity of opinion among cardiologists or obstetricians in regard to management. Since criteria for the care of these patients could not be based upon the limited experience of any one institution, a survey was undertaken of their management in the leading obstetrical centers throughout the country.

Questionnaires were sent to 300 hospitals, each with 2,000 or more deliveries per year. Replies were received from 102 of the institutions revealing a total of 113 cases of subacute bacterial endocarditis preceding or complicating pregnancy. These include the 12 cases[7-11] previously reported in the American literature. Fifty four per cent of those who responded stated that no case of this type had been delivered at their institution. However, there is no doubt that there have been many more instances than are reported in this series. In addition, 7 cases,[3-6] were collected from the British literature. This report, therefore, is based on 120 cases, 85 following healed subacute bacterial endocarditis, and 35 complicated by and cured of this disease during pregnancy.

TABLE I. MATERNAL MORTALITY IN 120 CASES OF HEALED SUBACUTE BACTERIAL ENDOCARDITIS DISTRIBUTED ACCORDING TO TERMINATION OF PREGNANCY

PARITY	EARLY SPONT. ABORTION		LATE SPONT. ABORTION		THERAPEUTIC ABORT. EARLY		THERAPEUTIC ABORT. LATE		VIABLE		TOTAL	
	NO.	MORT. %	NO.	MORT. %	NO.	MORT. %	NO.	MORT. %	NO.	MORT. %	NO.	MORT. %
Primiparas	2	0.0	2	50.0	6	0.0	0	0.0	68	4.4	78	5.1
Multiparas	0	0.0	0	0.0	7	0.0	1	0.0	25	4.0	33	3.0
Unknown	0	0.0	0	0.0	0	0.0	0	0.0	9	33.3	9	33.3
Total	2	0.0	2	50.0	13	0.0	1	0.0	102	6.8	120	6.6

As noted in Table I, there were 78 primiparas, 33 multiparas, and in 9 the parity was not stated. Four cases terminated in spontaneous abortions and in 14 therapeutic abortion was performed. One hundred two cases went to

viability with the loss of 3 infants, a viable fetal loss of 2.9 per cent. There were 3 maternal deaths in the healed group with a rate of 3.5 per cent, while the rate rose to 4.2 per cent when subacute bacterial endocarditis occurred during pregnancy. The maternal mortality rate for the entire series was 6.6 per cent.

Factors Influencing Prognosis

Once the cure of subacute bacterial endocarditis has been achieved, the basic problem, as far as pregnancy is concerned, reverts to the valvular abnormalities which pre-existed the infection and to the additional damage done during the healing process of the acute infection. In the majority of instances, subacute bacterial endocarditis occurs on already damaged valves or at the site of congenital defects (Tables II, III).

TABLE II. MATERNAL MORTALITY IN 105 CASES OF HEALED SUBAUTE BACTERIAL ENDOCARDITIS SUPERIMPOSED ON RHEUMATIC HEART DISEASE

DURATION (YEARS)	INCIDENCE		CARDIAC FAILURE		DEATH	
	NO.	%	NO.	%	NO.	%
Less than 10	12	11.4	0	0.0	0	0.0
10-14	28	26.6	1	3.5	1	3.5
15-18	30	28.5	3	10.0	1	3.3
20-24	13	12.3	3	23.0	2	15.3
25-29	4	3.8	0	0.0	0	0.0
Over 30	1	0.9	0	0.0	0	0.0
Unknown	17	16.1	5	29.5	3	17.6
Total	105	100.0	12	11.4	7	6.6

TABLE III. MATERNAL MORTALITY IN 15 CASES OF HEALED SUBACUTE BACTERIAL ENDOCARDITIS SUPERIMPOSED ON CONGENITAL HEART DISEASE

LESION	INCIDENCE		CARDIAC FAILURE		DEATH	
	NO.	%	NO.	%	NO.	%
Patent ductus	9	60.0	1	11.1	1	11.1
Septal defect	5	33.3	0	0.0	0	0.0
Aortic stenosis	1	6.7	0	0.0	0	0.0
Total	15	100.0	1	6.7	1	6.7

During the first six months following clinical cure, the cardiac reserve is not stabilized; valvular healing, as demonstrated by Moore,[12] is being completed and the danger of reactivation of the original infection is still present. It is generally conceded that cardiac decompensation and maternal death are most prone to occur if pregnancy supervenes during this period. Accordingly, of the six patients in this series who became pregnant during this time, four had therapeutic abortions preformed and only two were permitted to go to term. Of the latter, one case terminated fatally as a result of cardiac failure and recurrence of the infection during the puerperium and the other had an uneventful outcome. The increased maternal risk at this time is also evident from the high recurrence rate, the high failure rate, and the high mortality rate demonstrated in Table IV.

When bacterial endocarditis was treated during pregnancy, the maternal mortality rate was 14.6 per cent, almost six times as great as the 2.5 per cent found in the group healed for a long time. The patient cured for more than

6 months incurs a risk similar to that of any pregnant woman with cardiac disease and the management is determined solely by those factors which affect the outcome of any pregnancy complicated by heart disease.

TABLE IV. HEART FAILURE, DEATH, AND RECURRENCE OF SUBACUTE BACTERIAL ENDOCARDITIS ACCORDING TO INTERVAL BETWEEN CURE AND PREGNANCY IN 120 CASES

INTERVAL IN MONTHS	INCIDENCE		RECURRENCE		HEART FAILURE		DEATH	
	NO.	%	NO.	%	NO.	%	NO.	%
Less than 6	6*	5.0	2	33.3	1	16.6	1	16.6
6-11	4	3.3	0	0.0	0	0.0	0	0.0
12-24	18	15.0	3	16.6	0	0.0	0	0.0
25-36	22	18.3	1	4.5	0	0.0	0	0.0
37-48	9	7.5	0	0.0	0	0.0	0	0.0
49-60	8	6.6	0	0.0	0	0.0	0	0.0
Over 60	18	15.0	2	11.1	2	11.1	2	11.1
During pregnancy	35	29.1	0	0.0	10	28.5	5	14.2
Total	120	100.0	8	9.4†	13	10.8	8	6.6

*Four patients had therapeutic abortions.
†Based on 85 cases with clinical cure of more than 6 months' duration prior to recurrence.

Complications of Pregnancy

Cardiac Decompensation.—Congestive failure is of gravest import in pregnancy complicated by heart disease. The failure rate, as reported in the latest studies, varies from 0.99 per cent[13] to 17.6 per cent.[14] Decompensation rarely occurs prior to the twentieth week of gestation. Its incidence increases rapidly thereafter to reach a maximum in the eighth month. It rarely occurs for the first time during labor or the puerperium (Table V).

TABLE V. CARDIAC COMPLICATIONS DURING PREGNANCY IN 85 CASES OF HEALED SUBACUTE BACTERIAL ENDOCARDITIS

COMPLICATION	TOTAL DURING PREGNANCY	PRIOR TO PREG.	ANTE PARTUM ONLY	ANTE, INTRA, AND POST PARTUM	ANTE AND POST PARTUM	POST PARTUM ONLY
I. Cardiac failure	3	9*	0	0	1	2
Maternal deaths	3†	-	0	0	1	2†
Maternal death rate	100%	-	0.0%	0.0%	100%	100%
II. Embolism	0	9	0	0	0	0
Maternal deaths	0	-	0	0	0	0
III. Recurrence of S.B.E.	8	1	5	0	0	3‡
Maternal deaths	1†	-	0	0	0	1†
Maternal death rate	12.5%	-	0.0%	0.0%	0.0%	33.3%
Total complications	11	19	5	0	1	5
Total maternal deaths	3	-	0	0	1	2

*Includes 4 cases of therapeutic abortion.
†One associated with recurrence of subacute bacterial endocarditis.
‡All cases failed to receive prophylactic antibiotic therapy either intra- or postpartum. One followed a therapeutic abortion.

As a result of further damage done to already deformed valves during the healing process of bacterial endocarditis, one might expect an increased incidence of decompensation in subsequent pregnancies. This is not borne out by the findings of this study where a low failure rate was noted. Only 3, or 4.2

per cent, of the healed group who were permitted to continue with pregnancy beyond the twelfth week of gestation experienced failure and all of these cases terminated fatally during the puerperium. The risk of decompensation in the healed bacterial endocarditis is similar to that in any other pregnant patient with heart disease. The risk of fatal outcome, however, may be greater.

Recurrence of Subacute Bacterial Endocarditis.—Eight patients in the healed group had a recurrence of subacute bacterial endocarditis, an incidence of 9.4 per cent. Three cases recurred during the puerperium, each of which had not been treated by antibiotic therapy either during labor or following delivery. There were no recurrences in those patients who did receive antibiotic therapy during labor and the early puerperium (Tables IV and V).

The question to be answered is, "Does pregnancy increase the incidence or predispose to recurrence in the healed group?" It would be advantageous, therefore, to know the rate of recurrence in the nonpregnant individual followed for a similar period of time.

Cates and Christie[15] found a 2 per cent yearly recurrence rate in their series. Loewe[16] has followed 75 healed patients for a period of 5 to 6 years. In his series, there were 11 instances of recurrence, a rate of 14.7 per cent. Among this group, there were 27 women of childbearing age with a recurrence rate of 14.8 per cent. It appears, therefore, that pregnancy does not predispose to or increase the incidence of recurrence. The liberal use of antibiotics for febrile conditions during pregnancy and routinely during labor and the postpartum period will further decrease the possibility of recurrence.

Embolism.—Embolism is not likely to occur during the pregnancy in the patient with healed endocarditis. When the active infection complicates pregnancy, embolism may occur and is a manifestation of the infectious process. It is not related to pregnancy.

TABLE VI. DEVELOPMENT OF SUBACUTE BACTERIAL ENDOCARDITIS DURING PREGNANCY IN 35 CASES

TRIMESTER	NO. OF CASES	% OF TOTAL	CARDIAC FAILURE		RECURRENCE OF S. B. E.		DEATH	
			NO.	%	NO.	%	NO.	%
First	3	8.6	0	0.0	0	0.0	0	0.0
Second	15	42.9	4	26.7	0	0.0	1	6.7
Third	13	37.1	3	23.0	0	0.0	1	7.6
Unknown	4	11.4	3	75.0	0	0.0	3	75.0
Total	35	100.0	10	28.5	0	0.0	5	14.2

Active Subacute Bacterial Endocarditis Complicating Pregnancy.—In a pregnant patient with heart disease the occurrence of subacute bacterial endocarditis is a grave complication. The infection superimposed upon the load of pregnancy results in an increased rate of failure. This appears to occur most commonly when the infection develops after the twentieth week of gestation. Decompensation occurred in 10 of the 35 cases (28.5 per cent) and was 8 times as common as in the healed group. Only the five cases that terminated fatally had a recurrence of failure during the postpartum period. Following recovery from failure, hospitalization should be continued for the remainder of preg-

TABLE VII. CARDIAC COMPLICATIONS IN 35 PREGNANCIES COMPLICATED BY ACTIVE SUBACUTE BACTERIAL ENDOCARDITIS

COMPLICATION	OCCURRENCE OF COMPLICATION					
	TOTAL DURING PREGNANCY	PRIOR TO PREG.	ANTE PARTUM ONLY	ANTE, INTRA, AND POST PARTUM	ANTE AND POST PARTUM	POST PARTUM ONLY
I. Cardiac failure	9	0	4	4	1	0
Maternal deaths	5	-	0	4	1	0
Maternal death rate	55.5%	-	0.0%	100%	100%	0.0%
II. Embolism	4	0	3	0	0	1
Maternal deaths	0	-	0	0	0	0
III. Relapse of S.B.E.	0	-	0	0	0	0
Maternal deaths	0	-	0	0	0	0
Total	13	-	7	4	1	1
Maternal deaths	5	0	0	4	1	0

nancy regardless of the clinical cure of the subacute bacterial endocarditis and the original cardiac status. During the healing process, the cardiac classification usually shifts from a more favorable to a less favorable class (Tables VI, VII).

The impression that this is a rare complication of pregnancy must be revised in light of our data. The number of cases herein reported is greater than that found in a review of the world literature through 1941. Awareness that this disease may further complicate heart disease in pregnancy is the most important factor in establishing a diagnosis. It should be suspected in all such patients who run a febrile course, especially when decompensation is present. As in the nonpregnant individual, the prognosis becomes poorer the longer the interval between onset of symptoms and treatment. Jones and his associates[5] noted that there was often a delay of 1 to 3 months from onset of symptoms to diagnosis and treatment during pregnancy. In one patient, a delay of 3 months prior to seeking treatment contributed to a fatal outcome on the eighteenth postpartum day.

Intensive antibiotic therapy should be started as soon as the diagnosis is confirmed by positive blood culture. The treatment is as successful in the pregnant as in the nonpregnant individual. The concept of Dobson[9] that pregnancy has a deleterious effect on the course of the disease is not demonstrated in this series. Clinical cure of the subacute bacterial endocarditis was established prior to the twentieth week of gestation in only 4 of the 35 cases. It is our feeling that therapeutic interruption of pregnancy following cure should not be performed during the twelfth to the twentieth week for the hazard of the surgical procedure is as great a maternal risk, if not greater than the continuation of pregnancy.

Prenatal Care and Management of Labor

The prenatal care and management and conduct of labor appear to be similar to that of any patient with heart disease. Prenatal care is aimed at the prevention of decompensation, and delivery should be accomplished as easily as possible. Cesarean section should be performed only for obstetrical indications.

TABLE VIII. CONDUCT OF LABOR IN 102 CASES OF HEALED SUBACUTE BACTERIAL ENDOCARDITIS

		NUMBER OF CASES
Mode of Delivery.—	Not stated	7
	Spontaneous	29
	Low forceps	59
	Cesarean section	7
Analgesia.—	Not stated	12
	None	8
	Systemic	67
	Conduction	15
Anesthesia.—	Not stated	12
	None	5
	Local	23
	Conduction	25
	General	37

In the presence of an anesthesiologist, conduction anesthesia is the ideal analgesic and anesthetic agent. In absence of one, intramuscular Demerol analgesia and pudendal block anesthesia are the agents of choice (Table VIII).

Prophylactic Antibiotic Therapy

In order to prevent and minimize the occurrence of subacute bacterial endocarditis following parturition, all patients with heart disease, regardless of type, should receive prophylactic antibiotic therapy, commencing with the onset of labor and continuing into the postpartum period. Wheeler[17] found that abortion or delivery was the precipitating factor for the initial episode of subacute bacterial endocarditis in 16.7 per cent of his cases, and this was also true of 5 cases in this series. Most astonishing is the fact that 18, or 15 per cent, of the patients with healed subacute bacterial endocarditis received no antibiotic therapy either intra or post partum, and the 3 cases of postpartum recurrence were found among this group (Table IX).

TABLE IX. ANTIBIOTIC THERAPY IN 120 CASES OF HEALED SUBACUTE BACTERIAL ENDOCARDITIS

	NUMBER OF CASES
No antibiotic therapy	18
Antepartum, intrapartum and postpartum	46
Intrapartum only	2
Intrapartum and postpartum	39
Postpartum only	8*
Not stated	7
Total	120

*Postpartum antibiotic therapy was considered inadequate in 6 cases.

The drug of choice for prophylactic treatment in the puerperium is one of the broad spectrum antibiotics,[18] either terramycin or aureomycin. These drugs have a greater range of effectiveness on the flora of the postpartum uterus than does penicillin. This is confirmed by the work of Guilbeau and his associates[19, 20] who found that beta and gamma anaerobic streptococci and *E. coli* were present in penicillin-treated cases but absent in those treated with aureomycin. Whereas these organisms are etiological agents responsible for subacute bacterial endocarditis in many instances, those resistant to aureomycin, such as *Clostridium welchii* or *Proteus vulgaris* rarely are.

Therapy should commence with the onset of labor and consist of 500 mg. of terramycin or aureomycin every 6 hours by mouth. This should be continued for 72 hours. If these antibiotics are unavailable, aqueous crystalline procaine penicillin may be substituted to advantage. Six hundred thousand units of penicillin, intramuscularly, should be given at the onset of labor and, thereafter, 300,000 units, intramuscularly, twice daily for the first 5 days post partum. Penicillin is given for a longer period because of its more rapid excretion from the body and for a greater effect on those organisms that are moderately resistant to it.

Future Pregnancies and Therapeutic Abortions

Regardless of the patient's original cardiac status, pregnancy is contraindicated for the first six months following clinical cure of the subacute bacterial endocarditis. Pregnancy during this period of valvular healing and stabilization of the cardiac reserve is associated with an increased incidence of failure and maternal mortality. If it occurs, therapeutic abortion appears to be indicated prior to the twelfth week of gestation. By the same token, therapeutic abortion might be advantageously utilized in those cases where subacute bacterial endocarditis occurs and is cured during the first trimester of pregnancy. Tubal ligation in these cases is not warranted. When valvular healing is complete, the patient usually reverts to a more favorable cardiac classification and future pregnancies may be permissible (Table X).

TABLE X. INDICATIONS FOR THERAPEUTIC ABORTION IN 14 CASES OF HEALED SUBACUTE BACTERIAL ENDOCARDITIS

INDICATION	NUMBER OF CASES
Previous cardiac failure	4
Cure less than 6 months' duration	4
Healed S.B.E. more than 6 months' duration	4
Harmful effect of pregnancy on S.B.E.	1
Severe pyelonephritis	1
Total	14

Healed subacute bacterial endocarditis of longer duration per se is never an indication for therapeutic abortion. Pregnancy has no deleterious effect on and is permissible in cases of subacute bacterial endocarditis healed for more than 6 months. It is inadvisable to discourage pregnancy for many years following clinical cure, for, with the passage of time, the cardiac status will not only not improve but may deteriorate. The discouragement or interruption of pregnancy in this group should be based upon the severity of the underlying lesion.

Summary and Conclusions

1. Eighty-five cases of pregnancy following healed subacute bacterial endocarditis and 35 cases of pregnancy complicated by the development and cure of subacute bacterial endocarditis are reviewed.

2. The maternal mortality rate for the healed group was 3.5 per cent and for the group cured during pregnancy, 14.2 per cent. The maternal mortality rate for the entire series was 6.6 per cent.

3. Pregnancy following healed subacute bacterial endocarditis is contraindicated for the first six months following clinical cure. During this period, lack of stabilization of the cardiac reserve results in an increased incidence of congestive failure and an increased maternal mortality rate. If pregnancy occurs during this phase, therapeutic abortion without tubal ligation is indicated and should be performed during the first trimester.

4. Healed subacute bacterial endocarditis of longer duration per se is no contraindication to pregnancy. The advisability of childbearing is determined by a critical evaluation of the underlying cardiac lesion.

5. Pregnancy does not predispose to recurrence of the subacute bacterial endocarditis. The incidence of recurrence during pregnancy is similar to that noted in the healed, nonpregnant individual.

6. The treatment of subacute bacterial endocarditis is as successful in the pregnant as in the nonpregnant cardiac. Early diagnosis is the key to successful treatment.

7. The prenatal care and conduct of labor are similar to that in any patient with heart disease. Cesarean section should be performed only for obstetrical indications.

8. Routine intra- and postpartum use of antibiotics in all patients with heart disease is advocated to prevent the occurrence or recurrence of subacute bacterial endocarditis.

We wish to express our thanks and appreciation to our colleagues and their respective hospitals throughout the country without whose cooperation this study would not have been possible.

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A PELVIC STUDY: II. COMPLETE PELVIMETRY, INCLUDING THE USE OF A PROPOSED NEW SYSTEM OF PELVIC PROFILE DESCRIPTION*†

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PELVIMETRY is often regarded as the obtaining of a set of numbers representing measurements of certain diameters. Although much progress has been made in the past fifty years, we still see an occasional article where the prognostic values of a certain single diameter or a new type of pelvimeter are presented with claims that they will resolve all problems of disproportion. On the other hand, there are the enthusiasts for one or another method of clinical or roentgenological pelvimetry.

The present state of pelvimetry can be described as a hodgepode of terms, systems, and statistics which confuse the novice and which the expert cannot often translate into terms of practical obstetrics. In 1949, Colcher and Sussman[1] commented on a minimum of twenty internal pelvic diameters and six of the many different methods of roentgen pelvimetry.

It is a reasonable conclusion that pelvimetry is employed in the average obstetrical practice as a procedure with incidental measurements leading to a conclusion that the pelvis is "gynecoid." This is not the gynecoid pelvis of the Caldwell-Moloy classification, except by unknowing accident. It is the obstetrician's symbol that he "guesses" the pelvis is adequate in capacity for vaginal delivery.

The earliest pelvic evaluations were limited to external measurements. After repeated studies, it is now evident that these measurements are useless in practical obstetrics. The continued use of external measurements in pelvimetry is only a gesture toward tradition at the present time, usually enforced by outdated rules or standards.

With the advent of the roentgen tube, exact methods of roentgen pelvimetry were devised. Caldwell and Moloy employed the precision stereoscope and introduced a method of pelvic classification related to anthropological data. This has been extremely valuable and focused attention upon efforts toward evaluation of the internal capacity of the birth passage. Similar efforts by Thoms have given us a system of pelvic classification based on the index of inlet diameters, obtained by a simple, yet accurate method of roentgen pelvimetry.

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Since the precision stereoscope is not available, that method has not found general use and cannot be assayed for this reason. The method of Thoms and Wilson is generally used, occasionally with slight modifications described by later investigators.

During recent months, a series of 246 primiparous patients have been included in a pelvic study at this hospital. The experience consists of evaluation by clinical examination in the prenatal period, in labor and at delivery, and by roentgen pelvimetry, occasionally with roentgen studies in labor. This total evaluation has aroused our interest in complete pelvimetry as related to practical obstetrics. This experience has emphasized the confusion alluded to above, and has resulted in a proposed new system of pelvic profile description to be presented as part of this report. Employing the old inlet classification systems, the incidence of pelvic types in our series was as follows:

Class 1. Platypellic			15
Platypelloid	4	Platypelloid-gynecoid	3
Gynecoid-platypelloid	4	Anthropoid-platypelloid	2
Platypelloid-android	1	Platypelloid-anthropoid	1
Class 2. Brachypellic			132
Anthropoid-gynecoid	42	Platypelloid-android	5
Gynecoid	31	Platypelloid	3
Platypelloid-gynecoid	21	Platypelloid-anthropoid	2
Gynecoid-platypelloid	9	Anthropoid-android	2
Gynecoid-anthropoid	5	Android-anthropoid	1
Gynecoid-android	5	Android	1
Android-platypelloid	5		
Class 3. Mesatapellic			78
Anthropoid-gynecoid	33	Android-anthropoid	1
Gynecoid	18	Anthropoid-android	1
Anthropoid	10	Anthropoid-platypelloid	1
Gynecoid-anthropoid	6	Platypelloid-gynecoid	4
Gynecoid-android	2	Android-gynecoid	2
Class 4. Dolichopellic			16
Anthropoid	7	Gynecoid	1
Anthropoid-gynecoid	4	Platypelloid-anthropoid	1
Gynecoid-anthropoid	3		

From these data, it is evident that the anthropoid-gynecoid or round pelvis is the most common. This is further reflected in that the posterior half of the inlet is anthropoid in 103 of 246 instances and the anterior half gynecoid in 164 of 246 instances.

What does the inlet classification mean clinically? First, it has no clinical application in diagnosis of pelvic type. In this study, the examiners, who were either qualified obstetricians or supervised residents in training, made a correct diagnosis in only 31 instances, an incorrect diagnosis in 167 cases, and made no diagnosis in the other 34 cases. If putting a label as to "type of pelvis"

is to be related to the inlet classification, it appears that a roulette wheel might be more reliable than clinical examination. Fortunately, this is not the objective of clinical pelvimetry, a point in case for the present consideration.

Without belaboring statistics, these inlet classifications have little practical application as regards outcome of labor, method of delivery, and final result of the pregnancy. Despite the original hopes that a certain type of midpelvis and outlet might be associated with each inlet of the Caldwell-Moloy classification, this has not been true in practical obstetrics. The obvious fault of these systems is that they are defined only by the inlet, and the inlet is revealed only by roentgen studies. Such classifications are of interest in the considerations of large series of patients, but impractical in managing individual patients.

If our consideration next proceeds to the clinical aspects of pelvimetry, we must realize the limitations of this type of examination. An excellent presentation was made recently by Moloy[2] of a satisfactory approach to clinical pelvimetry. The chief advantage of this approach is the use of descriptive terms, rather than attempting precise definitions with absolute measurements. We are too ready to accept numerical values without basis in fact.

In actual practice, the most important outlet pelvimetry is that done in the delivery and labor rooms by means of sterile vaginal examination. As for the actual outlet measurements, the sacropubic diameter is identical with the anteroposterior diameter of the midplane for all practical purposes. Since transverse contraction rarely if ever occurs without similar midplane contraction, the interspinous diameter is a satisfactory measurement to relate to the outlet transverse diameter. These midplane measurements are accurately obtained with roentgen pelvimetry, and measurements therefor become unnecessary in clinical outlet pelvimetry. Clinical outlet pelvimetry finds its most useful role in evaluating soft tissue effects, elasticity of the perineum, and the shape and inclination of the pubic arch.

The report of Morris[3] is of interest. He evaluated the outlet with a cylindrical gauge with 9.3 cm. diameter. At full flexion at the outlet, the vertex most closely resembles a cylinder with all diameters averaging 9.3 cm. With extension, an oblique diameter of 10 cm. develops, so that a 10 cm. cylinder might be more critical in outlet evaluation. Basically, this is a refinement of the clenched fist measurement. A trial of some such cylinder might be considered in the intrapartum examinations done in a trial of labor.

The most important aspects of clinical pelvimetry relate to evaluation of the midpelvis. The splay of the sidewalls, the location and prominence of the ischial spines, the length of the sacrospinous ligaments, and the locations of the sacral tip relative to the depth of the posterior segment may be described.

However, at best we are left with an evaluation of the lower rim of the birth passage by our clinical examination. Complete pelvimetry requires both clinical and roentgen pelvimetry. With this combined approach, the inlet is evaluated by x-ray, the midplane by x-ray and clinical study, and the outlet by clinical study. Thus, complete pelvimetry is not exclusively one system, but a combination of the best of several methods.

The practical value of such complete descriptive study has been demonstrated in the accurate prediction of the probable mechanism of descent in labor. This skill was developed early in the course of the reported experience. Of the 246 cases, no prediction was attempted in 25 of the early cases, and the mechanism of labor was not observed subsequently in 41 other cases. However, of the total of 181 cases in which a prediction was made, followed by observation in labor, the prediction was correct in 165, better than 90 per cent correct. Compare this with the futile 12 per cent correct guess rate for clinical diagnosis of "type of pelvis."

One aspect of the complete study is the roentgen study of the pelvic curve of the sacrum. The nature of this curve is revealed only in the lateral x-ray of the pelvis, except in the small, generally contracted pelvis which permits palpation of the entire sacrum. The obstetrical significance has been discussed in the first part of this study, and the six basic types of curve described. These are:

J: The curve approximates that of the letter *J*.
H: The curve resembles a *H*ockey stick.
Si: The curve resembles that of a *Si*ckle.
A: The usual, regular curve shown in textbook illustrations.
Sh: A very *Sh*allow, almost flat curve.
St: A *St*raight, flat curve.

If the sacral curve is determined by roentgen study, and the location of the tip of the sacrum with reference to the ischial spines is determined clinically, one can readily visualize the location of the sacrum throughout its entire course. This is particularly important as the sacrum is occasionally either angulated anteriorly or inclined posteriorly, influencing greatly the space available in the posterior segment. This sacral curve often, therefore, has a determinant role in intrapelvic rotation, either as a part of spontaneous labor or in operative obstetrics.

Knowledge of the sacral curve is important in making prenatal predictions of the probable mechanism of descent in labor. Other factors for such predictions have been stated previously by Danforth,[4] that the biparietal diameter is the narrowest diameter and that the occiput tends generally to rotate to the widest point of the pelvis. With a thorough knowledge of any individual pelvis, plus these principles, one readily and accurately predicts the most likely mechanism of labor and the best possible solution to possible positional dystocia should that arise in labor.

The proposed pelvic profile description has been developed to assist in total pelvic evaluation, as a suggested solution to some of the deficiencies previously discussed. Thoms' classification system has been adapted and modified to include both the inlet and midplane. The inlet and midplane are coded by class according to the relationship of the anteroposterior and transverse diameters. The classes are:

1. Transverse diameter is 3.0 or more cm. greater than the A-P diameter (Thoms' platypellic).

2. Transverse diameter is 1-3 cm. greater than the A-P diameter (Thoms' brachypellic).
3. Transverse diameter is 0-1 cm. greater than the A-P diameter (Thoms' mesatipellic).
4. A-P diameter is greater than the transverse diameter (Thoms' dolichopellic).
5. A-P diameter is 0-1 cm. greater than the transverse diameter.
6. A-P diameter is 1-3 cm. greater than the transverse diameter.
7. A-P diameter is 3 or more centimeters greater than the transverse diameter.

Class 4 applies only to the inlet and Classes 5, 6, and 7 apply only to the midplane.

As an indication of the pelvic capacity, Mengert's midplane index has been selected. This is the multiple sum of the transverse and anteroposterior diameters of the midplane, determined by roentgen pelvimetry. Only rarely is the midplane larger than the inlet. The midplane is more important obstetrically with regard to borderline disproportion where pelvic evaluation is so important.

The proposed pelvic profile description is a coding system similar to the Pulhes physical profile employed by the armed forces of the United States and the United Kingdom. The profile of the pelvis has four elements. The first digit indicates the class of inlet; the second digit indicates the class of the midplane; the third factor is the letter designate for the type of pelvic sacral curve; and the fourth element is the midplane capacity index. To illustrate this coded profile, we may examine the most common profile in this series.

The final code would read 2 6 H 139. This indicates that the inlet transverse diameter is 1-3 cm. greater than the anteroposterior diameter and that the midplane anteroposterior diameter is 1-3 cm. greater than the transverse or interspinous diameter. The sacral curve resembles a hockey stick. The midplane capacity index is 139 which, by reference to suitably constructed tables, reveals the transverse diameter of the midplane to be 10-11 cm., and the anteroposterior diameter 12-13 cm.

Given such a profile, one should be able to visualize the shape and capacity of the entire pelvis, particularly when combined with a clinical examination of the lower midpelvis and outlet. This total or complete pelvic description is so much more practical than a name for an inlet shape, or a number for an outlet diameter.

After this description of the proposed new profile description system, its elements may be utilized in a presentation of the data of this study, with comment as to the incidence of the various elements.

TABLE I. THE DISTRIBUTION OF INLET AND MIDPLANE CLASSES

INLET CLASS / MIDPLANE CLASS	1	2	3	4	MIDPLANE TOTALS
1			1		1
2	1	3	1		5
3	3	21			24
5	8	46	21	1	76
6	3	63	49	9	124
7		5	6	6	17
Inlet totals	15	138	78	16	247

In Table I, the incidence of the classes of inlet and midplane are tabulated to show the distribution separately and in combination. Class 2 is most common at the inlet, and Class 6 most common at the midplane. In Table II, the incidence of the various types of sacral curve is shown in relation to the inlet and midplane classes. In Table III, the distribution of the various types of sacral curve according to the patient height and the midplane capacity index (Mengert) is shown. The data relative to the sacral curve have been considered in greater detail in Part I of this report.

TABLE II. THE INCIDENCE OF TYPE OF SACRUM FOR DIFFERENT INLET AND MIDPLANE CLASSES

	Type of Sacral Curve					
	A	sh	si	H	st	J
Inlet Class.—						
1	1	2	1	4	2	5
2	25	24	18	32	23	16
3	13	16	5	17	16	11
4	4	4	3	1	3	1
Total	43	46	27	54	44	33
Midplane Class.—						
1				1		
2	1			2		2
3	7	4	3	6	3	2
5	10	17	7	16	14	13
6	21	23	14	23	24	16
7	4	2	3	6	3	

TABLE III. THE INCIDENCE OF TYPE OF SACRUM FOR DIFFERENT PATIENT GROUPS ACCORDING TO HEIGHT AND TO MIDPLANE INDEX

	Type of Sacral Curve						
	A	sh	si	H	st	J	TOTAL
Patient Height.—							
Less than 5′ 2″	11	12	8	15	27	13	86
5′ 2″, but not 5′ 6″	23	23	14	27	27	22	136
5′ 6″ and over	9	11	5	12	8	2	47
Midplane Index.—							
100-119	9	9	4	6	3	8	39
120-139	16	16	8	22	18	13	93
140-159	17	17	13	17	20	9	93
160, plus	1	4	2	9	3	3	22

In 178 of the patients studied, it was possible at the time of labor to determine the position of the presenting vertex at both inlet and midplane. These data are shown in Table IV, with reference to the inlet and midplane classes, and in Table V, with reference to the type of sacral curve and midplane index.

These data reinforce previous observations. The vertex is most commonly in occiput transverse at engagement. The flat or Class 1 pelvis in particular is associated with occiput transverse position, and this persists at the midplane when the transverse diameter is greater. Likewise, the greater the anteroposterior diameter at the midplane, the greater the tendency toward occiput posterior position.

It might be appropriate at this point to express the opinion that shape of the outline of the bony pelvis has little influence on the position adopted by

the descending vertex. This is certainly true in the majority of deliveries, where the principles of Danforth, previously mentioned, prevail. Shape appears to be of importance perhaps in abnormal presentations such as face or brow, and occasionally in positional dystocia. Instead it is the available diameters for the fetal cylindroid that determine position and possibility of descent where the cephalopelvic relationships are borderline.

TABLE IV. THE POSITION OF THE PRESENTING VERTEX AND THE INLET AND MIDPLANE CLASS RELATIONSHIP

	Position			
	TRANSVERSE	OBLIQUE	POSTERIOR	ANTERIOR
Inlet Class.—				
1	13		1	
2	73	17	11	
3	34	13	9	
4	4		3	
Midplane Class.—				
1		1		
2	2	1	1	
3	12	5		1
5	27	23	6	1
6	43	33	9	1
7	4	5	3	

TABLE V. THE POSITION OF THE PRESENTING VERTEX AND THE RELATIONSHIP TO DIFFERENT TYPES OF SACRAL CURVE AND THE MIDPLANE INDEX, FOR BOTH INLET AND MIDPLANE

	Position of the Presenting Vertex					
	INLET			MIDPLANE		
	TRANS.	OBLIQ.	POST.	TRANS.	OBLIQ.	POST.
Type of Sacrum.—						
H	30	9	5	24	16	4
A	15	9	5	10	14	4
Sh	22	2	6	18	7	5
Si	16	2	1	8	0	3
St	20	6	5	20	8	2
J	19	2	3	16	6	2
Midplane Index.—						
100-119	23	4	5	19	9	4
120-139	54	9	8	43	21	4
140-159	38	12	8	28	22	9
160, plus	7	5	3	6	6	3

Kaltreider[5] recently reviewed his experience with different methods for evaluation of the inlet. His conclusion was that inlet evaluation cannot be strictly scientific as regards any particular area or index. This evaluation, to be sound, requires a combination of trial of labor and the judicious use of clinical examination, roentgen pelvimetry, and obstetrical judgment. This reinforces the concept of Mengert[6] of the determining components of cephalopelvic disproportion: (1) pelvic shape and capacity, (2) force of uterine contractions, (3) position of the presenting part, (4) moldability of the vertex, and (5) size of the fetus.

In other words, the determination of the intricacies of labor mechanics and end result depend on more than an inlet outline, a particular diameter, or any

one single denominator. A total appreciation of the pelvis, the fetus, the character of the labor, and the patient is required to be combined with fine obstetrical judgment. This is particularly true in the management of individual patients, as contrasted to discussion of a series or statistical analysis.

Interesting observations can be made relative to body height and pelvic capacity. The 64 patients of short stature provided 20 eventful deliveries consisting of 4 breech presentations, 3 (of 5) sections, 2 difficult occiput anterior positions, 2 persistent occiput posterior positions, and 9 persistent occiput transverse positions. For the 47 tall patients, only 10 deliveries were eventful, and of these only one occiput posterior was difficult.

The largest pelvic capacity index was in a patient under five feet in height. Height is not the indicator of pelvic capacity. With the index 100-119, 19 eventful deliveries were encountered; with index 120-139, 22 eventful deliveries occurred; with index 140-159, 13 eventful deliveries; and, with index over 160, only 5 eventful deliveries occurred, but only one was accompanied by any actual difficulty.

We expect more difficulty with the short-statured patient, and those in whom the pelvis is of small capacity. Likewise, the tall patient and the one with a large-sized pelvis have little obstetric difficulty. The uncomplicated and easy delivery of half of the occiput posteriors and half of the breech presentations in the whole study is consistent with previous observations and expectations.

The really significant fact is that 35 of the 57 eventful deliveries occurred when the pelvis was of medium capacity with index of 120-139. In particular, 3 of the 5 sections for disproportion, and 4 of the 11 difficult forceps deliveries occurred in this group. What further evidence is required to demonstrate that there is more to obstetrics than just the calculation of a diameter, an index, or an area?

MacLennan's report[7] is pertinent. It concerns a considerable experience with the contracted pelvis resulting from rickets. He was impressed most by the slightly contracted pelvis. First, it so frequently escapes clinical detection and becomes a problem in labor. Second, severe contraction becomes less important as diet eliminates rickets, and therefore the slightly contracted pelvis will become common, the contracted pelvis rare. Certainly our present study indicates the validity of this observation in that the majority of our "eventful" deliveries occurred in pelves of medium capacity.

Savage[8] correlated clinical and roentgen findings and described a dystocia clinic devoted to patients thought to be potential problems. Significantly, only 42 per cent of the patients thought clinically to have contracted pelves actually had them by roentgen pelvimetry. When the clinical and roentgen evaluations were combined for a total evaluation, their predictions, like our experience, were correct in over 90 per cent of cases. Savage made only limited comments about patients not attending his special dystocia clinic. He did not state the incidence of dystocia in the general clinic patients.

The question should be asked, "Can we select by clinical evaluation alone those patients who need total evaluation including roentgen pelvimetry?" This

practical question has been answered by this study. With a progressive shortage of naval personnel, particularly x-ray technicians, we have not been able to obtain roentgen pelvimetry with freedom. We were therefore forced to attempt clinical selection of potential problem patients.

In a group of 150 consecutive primiparous deliveries, review indicated that 32 patients had been selected for total study as potential problems in labor. Only 3 of this group actually had other than uncomplicated spontaneous or simple outlet forceps delivery. In contrast, of the 118 patients judged clinically to have adequate pelves and not to be deserving of total pelvic evaluation, 19 actually had eventful deliveries!

We know that 80 per cent of patients deliver uneventfully. As indicated in this study, we are unable clinically to select the individuals who will have eventful or problem deliveries. One-half of the problems are associated with pelves of medium capacity. It is in this group of patients with slight pelvic contraction and borderline dystocia that complete knowledge of the entire pelvis is so important to judicious obstetric management. The large pelvis is obviously no problem, and the very contracted pelvis presents obvious difficulties. The subtle problems of the pelvis of medium capacity or the slightly contracted pelvis require as complete knowledge as possible and as great obstetric skill and judgment as possible.

These facts show that a complete pelvic examination is essential for every patient. This includes roentgen pelvimetry with the determination of the pelvic profile description herein proposed. It also includes clinical pelvic examination, and observation and examination during labor, including the free use of roentgen studies in labor when necessary to assist clinical findings.

Except for the use of roentgen pelvimetry, such total pelvic evaluation is available to all patients. Roentgen pelvimetry needs be equally available to all. We do not hesitate to employ chemical determinations, serological studies, or extensive x-ray studies for the nonpregnant patient. Why should we fail to use roentgen pelvimetry, a laboratory aid that uses less than a dollar's worth of film and takes less than 10 minutes of a patient's time? What could be more simple, and yet yield so much valuable information for judicious obstetric management?

It is believed that use of the proposed pelvic profile description can do much to extend the use of x-ray pelvimetry as part of total pelvic evaluation. This makes it practical for a woman to have roentgen pelvimetry only once in her lifetime. Just as her blood type does not change, once determined, so the pelvic profile will remain unaltered.

Many communities now have a single laboratory for serology and bacteriology or chest x-ray examination. It is suggested that an enlightened public health program can provide x-ray pelvimetry for all women in a similar manner. The pelvic profile description thus obtained could be utilized by any obstetrician anywhere in combination with his clinical findings and observations to give a total pelvic evaluation.

Most important, this same information could be utilized in the care of the multiparous patient. The multipara is frequently slighted unless her first

delivery ended in section for one reason or another. Indeed, this profile could be adapted for the collection and analysis of data regarding the mechanism of labor and method of delivery for large groups of patients at different clinics. Such analysis could be profitably employed to follow patients through several pregnancies instead of our present customary limitation of consideration to the first pregnancy.

Finally, the study and the proposal of the pelvic profile description as part of total or complete pelvimetry indicate that obstetrics is not static. It is hoped that the facts reported and the suggestions offered will help to establish a dynamic concept of the problems of obstetrics in general, and pelvimetry in particular. Total or complete evaluation is recognized as being important, but the proposed profile description of the pelvis in code form offers a convenient, inclusive, and simple means of cataloguing information for purposes of practical obstetrics as well as for the exchange of data in a form not previously utilized.

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CONTINUOUS INTRAVENOUS INFUSION OF DEMEROL IN LABOR*†

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SINCE 1949, Demerol has been used intravenously at Cumberland Hospital. In a previous report,[1] the intravenous use of Demerol in the second stage of labor was cited in a series of 339 cases. To date this technique has been carried out in well over 2,500 cases without any untoward effect on the mother or infant and with as good analgesic-anesthetic effects as reported previously.

Demerol is used by most obstetricians by the intramuscular route and doses are repeated every four hours. Clinically, our observations agree with the experimental findings of Way and co-workers,[2] namely, that two hours after 100 mg. of Demerol is injected intramuscularly, there is no drug detectable in the blood. It had been our experience that the patients begin to complain of pain approximately one to two hours after the injection of Demerol intramuscularly. Therefore, our attention was directed toward the administration of small quantities (25 to 50 mg.) of Demerol given intravenously, hourly or every two hours, throughout the first stage of labor. There were no untoward effects on the mother or infant and good analgesic response was noted in the mother. However, this necessitated repeated puncture of the veins of the forearm and it was soon felt that intravenous administration of a weak solution of Demerol by drip probably would be the method of choice. In addition to the administration of analgesia, the patient would receive fluids during a period when liquids are generally restricted.

Much objection has been made to the use of intravenous Demerol because it was felt to cause a vasodilatation with a resultant hypotension.[3] We did not substantiate these findings as we have reported previously.[1] Recently, King and associates[4] reported on a physiological study of blood pressure changes during the intravenous administration of Demerol, and they agree that slow administration of Demerol to patients in the supine position is not associated with any severe circulatory changes.

This pilot, or preliminary, study included over 100 cases with good results. However, well controlled statistics were available on but 48 of these cases and these figures are presented.

Material

During the period November, 1951, to August, 1952, 48 patients who received Demerol by slow intravenous infusion had careful statistical evaluation of their progress in labor. The ages ranged from 17 to 36 years. There were

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18 nulliparas and 30 multiparas. All but two of these patients had attended our Antenatal Clinic for a period of three to five months. Complications existing at the onset of labor were as follows:

Polyhydramnios	1
Pre-eclampsia	3
Premature rupture of membranes	1
Essential hypertension with previous Manchester repair	1

The cases were unselected and all were delivered by the resident staff. Thirty-one patients were delivered by low or outlet forceps, 17 spontaneously. Thirty-three had episiotomies performed. Complications and surgical procedures during labor were noted as follows:

Laceration, perineal, first degree	2
Rotation by forceps	1
Rotation, manual	4
Breech, assisted	1
Uterine inertia	4
Manual removal of placenta	1

Procedure

In patients who are in labor, analgesia is started as soon as the patient begins to complain of moderate to severe pains. This is noted usually when the patient has a cervical dilatation of 4 cm. At this time, 25 to 50 mg. of Demerol is given intravenously and, with the needle in place, a slow drip of 100 mg. of Demerol in 250 ml. of distilled water is started at the rate of approximately 15 drops per minute. (Fifteen drops equals 1 ml.; 1 ml. is equivalent to 0.4 mg. of Demerol.) One of the veins of the forearm is preferable to maintain the intravenous flow; in case the patient moves her arm, this obviates the need of a restraint.

The rate of flow is regulated by the physician in attendance in order to control the amount of Demerol administered. Fifteen drops per minute is usually sufficient for the average patient. However, to obtain the maximum analgesia with the minimum quantities of Demerol, personal supervision of its administration is necessary because of (a) its diversity of reaction in different individuals, and (b) dissimilarity of labors. In some of the patients, 50 to 100 mg. of Demerol was given at delivery time as the case warranted.

The analgesic effects of Demerol were classified under four headings from the objective observation of the patient during labor, as outlined by Brown, Volpitto, and Torpin,[5] and the over-all picture was then summarized for the entire labor.

Excellent	Showed no evidence of pain.
Good	Showed marked relief of pain.
Fair	Showed some relief of pain.
Poor	Showed no appreciable relief of pain.

The condition of the infants was judged by the length of apnea, the degree of cyanosis and activity, and the efforts needed for resuscitation. The following gradation, set up previously,[1] was followed:

Grade I: Included those who breathed spontaneously and required the usual aspiration of the upper airway with suction by means of a mucus trap catheter.

TABLE I. SUMMARY OF OBSERVATIONS FOR MULTIPARAS

TOTAL VOL. I.V. DRIP	CONC. DEM. 100 MG. IN	DOSAGE IN MG.				LENGTH OF ADMINISTRATION		DURATION OF LABOR				WEIGHT OF INFANT	
								1ST		2ND	3RD		
		INITIAL	DRIP	FINAL	TOTAL	HR.	MIN.	HR.	MIN.	MIN.	MIN.	POUNDS	OUNCES
300 ml.	250 ml.	25	120	0	145	4	19	12	40	9	6	7	4
100 ml.	250 ml.	25	40	0	65	1	20	12		20	5	7	3
175 ml.	250 ml.	25	70	0	95	2	25	5	45	10	10	7	8
180 ml.	250 ml.	25	71	0	96	2	7	6		7	7	6	9
130 ml.	250 ml.	25	52	0	77	1	50	2		20	5	7	1
350 ml.	250 ml.	25	140	0	165	5	20	9		20	5	8	12
200 ml.	250 ml.	25	80	0	105	3	15	6		30	5	8	4
250 ml.	250 ml.	25	100	0	125	4	0	9	45	30	5	8	5
120 ml.	250 ml.	25	48	0	73	1	40	2	55	15	30	7	5
110 ml.	250 ml.	25	44	0	69	1	0	11		4	5	6	14
160 ml.	250 ml.	25	64	0	89	1	42	8	30	12	8	7	0
150 ml.	250 ml.	25	60	0	85	1	45	5	45	15	5	3	5
250 ml.	250 ml.	25	100	0	125	3	20	5	40	3	4	6	4
250 ml.	250 ml.	25	100	0	125	3	10	13	30	15	2	8	6
250 ml.*	250 ml.	25	100	100	225	3	55	3	40	5	4	4	12
180 ml.	250 ml.	25	72	100	197	2	45	4	30	15	5	3	11½
130 ml.	250 ml.	50	52	0	102	2	0	5	30	10	5	7	11
75 ml.	250 ml.	25	30	50	105	0	50	2	45	10	5	8	12
120 ml.	250 ml.	25	48	0	73	2	5	5	20	15	5	8	9
180 ml.	250 ml.	25	70	100	195	3	25	9	45	10	5	7	15
225 ml.	250 ml.	25	90	0	115	3	20	10	15	15	5	6	13
100 ml.*	300 ml.	50	33	0	83	0	55	5	5	5	5	8	2
130 ml.	250 ml.	25	58	50	133	1	45	15	15	30	10	7	7
75 ml.	250 ml.	25	30	50	105	1	0	13	45	15	2	8	9
200 ml.*	250 ml.	50	80	0	130	2	45			15	10	3	5
150 ml.	250 ml.	25	60	50	135	2	0	5	45	15 A	6	4	8 A
										20 B		3	4 B
70 ml.	250 ml.	25	28	100	153	1	0	15		5	5	8	3
60 ml.	250 ml.	25	25	0	50	0	40	4		16	4	6	0
100 ml.	250 ml.	25	40	100	165	3	0	1	10	10	5	7	0
60 ml.	250 ml.	50	25	100	175	1	0	12		60	5	7	3

*Intravenous Pitocin administered by separate infusion.

TABLE II. SUMMARY OF OBSERVATIONS FOR PRIMIPARAS

TOTAL VOL. I.V. DRIP	CONC. DEM. 100 MG. IN	DOSAGE IN MG.				LENGTH OF ADMINISTRATION		DURATION OF LABOR				WEIGHT OF INFANT	
								1ST		2ND	3RD		
		INITIAL	DRIP	FINAL	TOTAL	HR.	MIN.	HR.	MIN.	MIN.	MIN.	POUNDS	OUNCES
300 ml.	250 ml.	25	120	0	145	4	10	8	30	40	8	6	7
250 ml.	250 ml.	25	100	0	125	2	40	11	15	25	2	7	2
200 ml.	250 ml.	25	80	0	105	2	30	6		25	5	7	6
250 ml.	250 ml.	25	100	0	125	2	50	8		50	5	7	11
150 ml.	250 ml.	25	60	100	185	2	0	11		10	1	6	8
300 ml.	250 ml.	25	125	0	150	4	0	7	50	25	5	7	10
100 ml.	250 ml.	25	40	50	115	0	45	12	20	10	5	3	15
100 ml.	250 ml.	50	40	0	90	1	0	3	30	30	5	7	10
90 ml.	250 ml.	25	36	100	161	1	12	7		12	15	7	5
175 ml.*	300 ml.	25	58	100	183	3	30	9	15	15	5	8	2
150 ml.	250 ml.	25	60	100	185	2	30	5	15	5	5	6	8
200 ml.	300 ml.	50	66	50	166	1	0	14		30	½	7	2
375 ml.	300 ml.	25	113	50	188	3	10	12		30	5	6	13
50 ml.	300 ml.	50	15	0	65	0	50	5	30	40	1	7	1
205 ml.*	300 ml.	25	62	100	187	2	0	8	10	15	15	6	11
250 ml.	250 ml.	25	100	0	125	2	30	13	40	10	5	7	14
250 ml.	250 ml.	50	100	100	250	4	0	11		10	5	7	11
30 ml.	250 ml.	25	12	100	137	0	30	5	5	10	5	8	10

*Intravenous Pitocin administered by separate infusion.

Grade II: Included those infants who required no oxygen but in whom spontaneous respiration, though delayed, occurred within 60 seconds of birth.

Grade III: Included infants requiring over 90 seconds of resuscitation and oxygen.

Grade IV: Included infants who required over 90 seconds of resuscitation and positive-pressure oxygen insufflation, or who showed asphyxia and cyanosis, and whose condition warranted treatment or follow-up by a pediatrician.

The progress of the patient, the administration of medications, etc., as well as the effect of the medication on the mother and infant were kept on a special form at the bedside. These observations are summarized in Table I for multiparas and in Table II for nulliparas. In Table III, a comparison of the average total amount of Demerol administered intravenously together with the average length of administration, and, finally, the average amount of Demerol given per hour is presented for the nulliparas, multiparas, and both groups combined.

TABLE III. COMPARISON OF AVERAGE VALUES FOR PRIMIPARAS AND MULTIPARAS

PARITY	AVERAGE TOTAL AMOUNT OF DEMEROL ADMINISTERED (MG.)	AVERAGE LENGTH OF ADMINISTRATION		AVERAGE AMOUNT OF DEMEROL (MG. PER HOUR)
		HR.	MIN.	
Nulliparas	147.0	2	17	64.4
Multiparas	119.3	2	34	47.7
Combined	133.1	2	25	56.1

Results

All patients showed response to medication and had relief of pain. Thirty-one patients (64.6 per cent) had excellent or good analgesia and 17 patients (35.4 per cent) had fair analgesia. The majority of the patients would sleep between pains and showed a slight to moderate amount of activity with each contraction.

There was only one infant who required over 90 seconds of resuscitation and positive-pressure oxygen insufflation. Two infants required over 60 seconds but less than 90 seconds of resuscitation and oxygen. Eight infants cried spontaneously but the cry, although delayed, occurred within 60 seconds of birth. Thirty-seven infants breathed spontaneously and required merely the usual aspiration of the upper airway with suction by means of a mucus trap catheter.

There were no stillbirths in this series but there was one neonatal death. This infant was the one mentioned previously who required over 90 seconds of resuscitation and positive-pressure oxygen insufflation. The infant had a spina bifida and died shortly after birth. Death was not attributable to Demerol.

There was no apparent effect upon the course of labor, nor upon the uterine contractions, as shown by tokodynamometer tracings done by one of our previous research fellows, and we do not believe that Demerol as used can cause a cessation of labor. The patients were fairly quiet, easily aroused by calling their names, and very cooperative. This was striking, as the greater portion of the patients delivered at our hospital are highly excitable, with

language difficulty, and present more of a problem to manage than the ordinary patient. With other forms of analgesics, the patients usually are more irrational and less cooperative, particularly toward the latter part of the first stage. In general, the third stage was not prolonged and the amount of bleeding was average. The uterus responded to the routine oxytocic regime. There was one manual removal of the placenta because of retention of approximately 30 minutes.

Thirty-two patients were given local anesthesia in the form of 2 per cent procaine pudendal block. Three were delivered under saddle-block anesthesia with the use of a hyperboric solution of pontocaine. The remaining 13 patients required no further anesthesia for delivery.

Comment

Recently, Jeffcoate and co-workers[6] reported that Demerol, "like so many other agents, can now be safely and advantageously given by drip infusion. . . A suitable solution is 300 milligrams of pethidine in 1,000 ml. of glucose saline. Individuals vary in their sensitivity so the infusion should be commenced cautiously and the speed of administration thereafter varied to suit the patient. . . Although rarely necessary, as much as 600 to 800 mg. can be given within 24 hours without apparent ill effects on either the mother or child."

Concurrently, although separately, we have devised a similar technique to that noted by Jeffcoate. In our early work we used solutions of 100 mg. of Demerol to 300 ml. of distilled water and later changed it to 250 ml., merely because it was simpler to prepare. In our series we never had occasion to give Demerol to a patient for as long as 24 hours.

A most satisfactory feature of this technique is that the patient is never stuporous and is able to respond to questioning and comply with instructions. Questioning of the patient on the day following delivery discloses that the patient was aware of what was occurring but that the pain was markedly diminished. Multiparas, in comparing the labor with previous ones treated with other forms of analgesia, remarked that this labor was the least distressing. Very little evidence of amnesia was elicited.

In this study the Demerol was diluted in distilled water and was given this way to demonstrate the effect of Demerol solely. We, however, have administered Demerol in solutions of 5 per cent glucose in distilled water as well as saline. Caution is stressed in the use of saline solutions because of the retention of salt in pregnancy, especially in toxemia cases. Demerol and scopolamine in dilute solutions have also been used. The scopolamine enhances the analgesic effect of Demerol and produces amnesia. Recently, a 5 per cent solution of alcohol in glucose to which Demerol and occasionally scopolamine have been added has given more promising results. A sedative as well as an analgesic effect is obtained and the caloric content is most useful in the patients in labor.

Although we have used solutions of Pitocin together with Demerol in the same mixture, at this time we advocate having two separate solutions and infusions to get a more "individualized" dose administered to the patient for

each of these substances. We are attempting to standardize a solution in which the various drugs can be mixed for optimal effects.

Although the series presented is small, it is merely a preliminary or pilot study. A more extensive study will be presented at a later date.

Summary

A simple method for the administration of Demerol intravenously is presented. The amounts of medication are relatively small and result in a satisfactory maternal analgesic effect. The infants are not depressed upon delivery. Further investigation is now in progress utilizing alcohol and scopolamine to enhance the analgesic effects of Demerol and to provide amnesia as well.

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A PROPOSAL FOR LOWERING CESAREAN SECTION INCIDENCE: A VOLUNTARY AND EDUCATIONAL METHOD FOR STAFF CONTROL*

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STAFF members of voluntary hospitals at some time or other have had to face the problem of cesarean section on their obstetric service, and means to combat a high or rising incidence. The most customary solution has been the requirement of compulsory consultation on all cesarean sections, regardless of the rank of the staff member on the obstetric service. This mandatory policy, while excellent for "open staff" hospitals, is subject to much criticism in the "closed staff" hospital, where each man is a qualified, competent obstetrician.

The Obstetric Staff at the Jewish Hospital of Brooklyn was faced with just this problem in the year 1948. This paper is presented to acquaint our colleagues with a method selected by our Obstetric Staff, to reduce the cesarean section incidence if possible, and to crystallize the indications for this operative procedure, which no one can deny are broadening continually.

The aim of the method to be presented was primarily educational; the element of censure or criticism of a specific case or physician was not the objective at any time. The formulation of a rational set of policies regarding cesarean section indication that would govern the activity of the staff was the main purpose. If a decreased incidence of section operations could also be achieved, without sacrificing good and conservative obstetric practice, so much the better.

Toward this goal, a Cesarean Section Review Committee was appointed. In order to reflect a cross section of staff judgment, the Committee consists of an attending obstetrician as chairman, together with one associate and one assistant attending as members. The Committee has a sliding scale membership, that is, each six months one member is dropped and a new member is appointed in his place. The new appointee holds the same staff rank as the man just dropped. Thus, the continuity of the Committee's activities is preserved without perpetuating the initial membership, and also, in due time, each staff member will have an opportunity to serve.

It is the duty of the Committee to review each section chart each month. Selection is then made of certain cases which in the opinion of the Committee were unnecessary or wherein the indications were equivocal or wherein certain chart inadequacies failed to justify the procedure. The selected cases are then

*Presented at a meeting of the Brooklyn Gynecological Society, Jan. 23, 1953.

presented to the entire Staff at a special Cesarean Section Review Conference, held monthly. Attendance of the Staff at these conferences is obligatory. If a case of a nonobstetric staff member is to be discussed, that physician is so notified by letter, and his attendance is mandatory. Upon presentation of the case report to the Staff, the Committee Recorder also gives the reasons for selection of the specific case. General discussion is then held, and, finally, the obstetrician whose case is under discussion is heard from.

Review of the minutes taken by the Committee Recorder reveals that the Obstetric Staff, through their discussions at these monthly conferences, have established the following policies to be followed before cesarean section is resorted to:

I. Charts.—All charts on which sections are done should have the following data in detail:

a. Complete preoperative note with indication for the procedure.
b. A description of the pelvis, clinically or radiologically, sufficient to give a clear picture of the fetopelvic relationship.
c. A well written-up operative procedure giving pertinent findings such as location of placenta in cases of placenta previa, description of the uterine wall in cases of ablatio, location of fibroids, cysts, etc.
d. Cases seen by a consultant preoperatively should have a complete consultation note dictated by that consultant.

II. Cephalopelvic Disproportion.—

a. Elective section for this indication is rarely justified without a test of labor.
b. Radiologic evidence of disproportion alone is not sufficient to warrant elective section. The x-ray should be used only as an *adjunct* to clinical judgment.

III. Test of Labor.—Presumes the following:

a. Membranes must be ruptured.
b. Good labor has ensued for a reasonable number of hours, without progress in cervical dilatation or descent of the presenting part.

IV. Uterine Insertia or Dystocia.—It is becoming more apparent that a judicious trial of intravenous Pituitrin in selected cases under close observation will reduce the incidence of sections done for uterine inertia.

V. Toxemia of Pregnancy.—Wherever possible, toxemia cases should be medically treated and observed for a reasonable period of time before resorting to section.

VI. Placenta Previa.—In most suspected cases of placenta previa there should be a sterile vaginal examination for diagnostic purposes before section is resorted to. A definite diagnosis of placenta previa cannot be made without vaginal examination unless incontrovertible soft-tissue x-ray delineation of the placenta is present.

Comment

Table I reveals that, while the over-all section incidence remains static at about 5.5 per cent for the five-year period covered, there has been a 25 per cent reduction in the primary section incidence from 4.4 per cent to 3.3 per

cent. In addition, it should be pointed out that the over-all section incidence of 5.5 per cent at this hospital compares most favorably with the reported incidence from other large voluntary hospitals in the urban area, where section incidence varies to a high 13 per cent.

TABLE I. INCIDENCE OF CESAREAN SECTION IN THE YEARS 1948 TO 1952

	1948	1949	1950	1951	1952
Total deliveries	4,715	4,673	5,123	5,226	5,108
Total sections	272	244	272	291	288
Repeat sections	61	64	78	101	116
Incidence.—					
Uncorrected	5.7%	5.2%	5.3%	5.5%	5.6%
Corrected (For Repeat Sections)	4.4%	3.8%	3.7%	3.6%	3.3%

It is also to be mentioned that Table I fails to bring out a most important point, that some staff members used section as a solution to obstetric problems much more liberally than others. Thus, one of the major reasons for decision of staff education and control was to equalize the incidence of the operation among the staff and in this way contribute to general over-all lowering of the primary section incidence. It is felt that the 25 per cent lowering of primary section incidence in the four-year period shows that this has been achieved.

Perhaps the greatest achievement was the acceptance by the staff of a uniform set of policies, devised actually by themselves, in the course of discussion at the cesarean section conferences. These have been previously quoted. It must be understood that these policies are still incomplete, and will be amplified or revised as future case discussions may determine.

Recent literature[1, 2] has indicated the definite liberalization of indications for section throughout the country. This increased use of cesarean section may be the result of the increased safety of the operation, a better understanding of the mechanism of labor, or the recent statistical reports on infant mortality and birth injury. On the other hand, the judicious use of intravenous Pituitrin in properly selected cases is a counterbalancing influence, which may prevent the incidence from rising too sharply.[3, 4]

In conclusion it is stated that we have presented a five-year experience with a noncompulsory educational method of staff control for lowering cesarean section incidence. The friendly, informal nature of this method has proved attractive to the staff. A reduction of primary section incidence of almost 25 per cent has been noted in a four-year period. We propose to continue this method of self-censure in the future because we feel that this method of "thinking out loud" has induced men to change their methods of thinking.

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DIABETES IN PREGNANCY

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DIABETES has long been notorious for producing a high incidence of maternal complications related to acidosis and infection, and for its high fetal mortality. When the advent of insulin brought acidosis under control, Hurwitz and Irving[1] in 1937, and Mengert and Laughlin[2] in 1939, demonstrated that fetal loss could be substantially reduced. There the matter rested for fifteen years, perhaps because the relatively small numbers of diabetics appearing at obstetrical clinics failed to arouse much interest. With an increasing proportion of juvenile diabetics reaching the childbearing age, the subject has again become a problem of major obstetrical concern.

In the early 1940's Priscilla White[3, 4, 5] began to apply the work of the Smiths on the female sex hormones to the specific field of the diabetic woman. She was followed by Palmer, Crampton, and Barnes,[6] Jordan,[7] Randall,[8] and others. White's brilliant presentation[9] in 1947 focused attention on the possibility of improving fetal salvage by correcting hormonal imbalance. The literature on the subject is now in a state of flux, and writers are grouping into "hormone" and "nonhormone" schools of thought. (For brevity "hormone" here refers to any sex hormone, natural or synthetic.) The controversy is further complicated by conflicting views as to the proper time and method of effecting delivery of the pregnant diabetic patient. It is clear that four fundamental questions have to be answered:

1. What can be expected of the outcome of a diabetic pregnancy, in competent obstetrical hands, under good medical management on insulin alone, without the use of hormones?
2. What additional advantages are gained by using hormones; and, if any, in what types of cases?
3. Having carried the diabetic to viability, with or without hormones, what is a sound policy with regard to time of delivery?
4. By what method can delivery best be accomplished?

Comparative Statistics

Existing statistics are difficult to correlate because of wide variations in the incidence of acidosis and toxemia, section rates, and fetal salvage. A number of factors becloud evaluation of the literature. One is the fact that diabetes in pregnancy is so uncommon that many published series are too small to have statistical significance. Other difficulties are presented by the inclusion of prediabetic pregnancies, abortions, and cases delivered elsewhere. All these build up the reported group, but confuse the picture.

If we are to evaluate fairly the results of hormone management, we must have a clear concept of what can be accomplished without hormones. For a sound analysis, computations should be based solely on viable fetuses of diabetic women delivered in the reporting hospital. Reis, DeCosta, and Allweiss[10] reported 163 pregnancies, of which 59 fulfill these criteria. To date there are only three "nonhormone" reports from obstetrical services containing a hundred or more such cases: Given, Douglas, and Tolstoi[11] with 114; Hall and Tillman[12] with 107; and Hurwitz and Higano[13] with 124. This study adds 162 cases to that cumulative experience.

Material

The Providence Lying-In Hospital is one of the half-dozen largest obstetrical services in the United States. This report covers the twenty-five-year period, 1927-1951, comprising 100,962 deliveries. One hundred eighty-four diabetic pregnancies were observed (Table I). Eight early spontaneous abortions and one patient who left the clinic to deliver elsewhere are eliminated from the computation. Another 13 cases are likewise not counted because they received substantial doses of hormones. One hundred and fifty-eight cases reached viability (960 grams) without any hormone therapy; and 4 received doses (daily equivalent of 50 mg. stilbestrol or less, for varying periods of time) not considered clinically significant. This series of 162 nonhormone cases is studied in an effort to determine what can be done on an orthodox regime, and to find out where results can be improved.

TABLE I. 184 CASES OF DIABETES IN PREGNANCY

Nonviable pregnancies (abortions) under 960 grams	8	
Left clinic, delivered at home	1	
Received substantial doses of hormone therapy (over 75 mg. stilbestrol or equivalent daily)	13	
		22
Subclinical doses of hormone (less than 50 mg. stilbestrol or equivalent for varying periods)	4	
No hormone therapy	158	
"Nonhormone" series used in this study		162
Total diabetic pregnancies in 25 years (100,962 deliveries)		184

Miscellaneous Statistics

One hundred seven women carried these 162 pregnancies. Forty-one were primiparous (25 per cent) and 121 multiparous (75 per cent). There were 8 Negro (4.9 per cent) and 7 Jewish (4.3 per cent), reflecting the small number of these races in this New England community. There were 4 minor or correctable anomalies, and 6 incompatible with life, for a total of 10 (6.2 per cent). Of three sets of twins, one premature pair died and two pairs survived. This makes it possible to count twins as a unit when tables are arranged on the basis of pregnancies. There were 20 breech presentations in single pregnancies (12.1 per cent); counting twins, there were 23 breeches among 165 infants (13.9 per cent). Table II demonstrates that congenital anomalies were three times, breech and other malpositions three and one-half times, and

prematurity (both living and stillborn) four times the frequency of the last five-year rate for the hospital.

There were no maternal deaths in these 162 cases. The only death of a diabetic mother was in the nonviable group. This five months pregnant woman was admitted as an emergency in 1927, after having been sick at home for three weeks. She was in coma, and died undelivered four hours later. Autopsy showed bronchopneumonia, multiple lung abscesses, diabetic interstitial nephritis, and syphilis.

TABLE II. RELATIVE INCIDENCE OF COMPLICATIONS

COMPLICATION	5 YEAR (1946-1950) HOSPITAL INCIDENCE 34,833 INFANTS IN 34,480 DELIVERIES		DIABETES 165 INFANTS IN 162 DELIVERIES		DIABETIC INCREASE
Breech presentation	1,412	4.0%	23	13.9%	×3.5
Total malpositions (breech, transverse, compound)	1,484	4.2%	25	15.1%	×3.6
Congenital anomalies	731	2.1%	10	6.6%	×3
Prematurity (2 pounds, 2 ounces, to 5 pounds).—					
Live birth	1,198	3.4%	17	10.3%	
Stillbirth	159	0.5%	9	5.4%	
Total premature	1,357	3.9%	26	15.7%	×4
Correcting out premature induced delivery or section			22	13.3%	×3.4
Correcting out fetal loss and prematurity in acidosis and toxemia			6	3.6%	none

Abortions

This is an obstetrical hospital; only 2.0 per cent of the 103,037 admissions in this period were for abortion. There was no therapeutic abortion for diabetes. From this small experience we can only say as to incidence that: Of 88 multiparas with reliable lifetime history, there were 28 abortions in 372 pregnancies (7.6 per cent). Of 92 multiparas whose histories are reliable during the known period of diabetes, there were 17 abortions in 175 pregnancies (9.8 per cent). Recent writers on the subject[12, 14, 15, 16] report an average of 10 per cent. It would thus appear that diabetics do not abort more frequently than do normal women.

Viability

Viability can be expressed on the basis of weight, or by weeks of gestation. White's criterion of 960 grams (2 pounds, 2 ounces) is here used for comparison with her results for fetal survival. This is a low standard, and carries with it a high loss from prematurity alone. For the five-year period, 1947-1951, the gross loss in our premature nursery among infants between 2 pounds, 2 ounces, and 3 pounds was 61.9 per cent; and from 3 pounds, 1 ounce, to 4 pounds it was 26.4 per cent. This does not include the infants who died in the delivery rooms without reaching the nursery. This wastage must be considered when studying fetal death. It is an inevitable loss not attributable to the maternal diabetes itself.

Acidosis

The outcome of a diabetic pregnancy hinges on control of the diabetes. It is on this point that reports from obstetrical services must differ from those of diabetic clinics. White and other internists, who are reporting the results in selected cases, are dealing with trained, cooperative, and superbly supervised women. The preventable types of break in control are not likely to occur. They do not see the unrecognized diabetics. Nor do they report the end results of the uncooperative patient who drifts away from control, eventually to deliver on some obstetrical service, to the detriment of its fetal loss statistics. It is hard to accomplish the ideal of having no acidosis. Every obstetrical hospital acquires the emergency cases, the uncooperative patients, the women inadequately managed by physicians unfamiliar with the vagaries of diabetes in pregnancy, and the difficulties encountered when a practitioner attempts to conduct both the obstetrical and the medical care.

TABLE III. ACIDOSIS—CAUSES AND FETAL LOSS

CAUSE OF BREAK IN CONTROL	CASES	% ALL ACIDOSIS	FETAL LOSS	
1. Uncooperative patient	15	34.1	9	80.0%
2. Inadequate medical supervision	10	22.7	7	70.0%
3. Undiagnosed until in acidosis	5	11.4	3	60.0%
4. Intercurrent infection	8	18.2	2	25.0%
5. "Brittle" diabetic under competent medical supervision	6	13.6	2	33.3%
All acidosis	44	100.0	23	52.3%

The preventable acidosis in categories 1, 2, and 3 represents 68.2 per cent of all acidosis, and accounts for 39.6 per cent of the gross fetal loss in diabetes.

There were 44 cases of acidosis in this series, an incidence of 26.9 per cent. Of these 29 were mild (66.0 per cent), 12 severe (27.2 per cent), and 3 in coma (6.8 per cent). The gross fetal loss was 23 infants (52.3 per cent). The preventable types of acidosis indicated in Table III represent 68.2 per cent of all acidosis, and account for 39.6 per cent of the whole diabetic fetal loss. Nineteen infants were lost in patients with acidosis due to their own carelessness, inadequate medical care, or unrecognized diabetes. Congenital anomaly accounted for death in 2 of these; toxemia was a major complication in 4 others; in the remaining 13 cases the acidosis was the primary cause. If these 13 infants had been salvaged, the loss in acidosis would be more than halved to 22.7 per cent, and the gross fetal loss for the series reduced to 21.6 per cent.

TABLE IV. ACIDOSIS—RELATIONSHIP OF SEVERITY OF DIABETES TO SEVERITY OF ACIDOSIS

SEVERITY OF DIABETES	SEVERITY OF ACIDOSIS AND INCIDENCE			FETAL LOSS	
Mild Diabetes (103 Cases)	Mild acidosis	16 cases	15.5%	6	37.5%
	Severe acidosis	4	3.9%	4	100.0%
	All acidosis	20	19.4%	10	50.0%
Severe Diabetes (59 Cases)	Mild acidosis	13	22.0%	7	53.8%
	Severe acidosis	11	18.8%	6	54.4%
	All acidosis	24	40.8%	13	54.2%
162 Diabetics	Total acidosis	44 cases	27.2%	23	52.3%

Severe acidosis carries a high fetal mortality in mild diabetes, and any degree of acidosis is lethal in severe diabetes.

Given[11] was impressed by the fact that 41.7 per cent of his nontoxic patients whose infants died in utero had experienced ketoacidosis. Hall and Tillman[12] had a 66.6 per cent fetal loss in the presence of acidosis, with at least 9 other cases in which subclinical acidosis might have explained fetal death. They point out that "since the fetus is so sensitive to temporary alterations in maternal pH, it is not unlikely that this mechanism explains many cases of premature delivery and death in utero." With this we agree. Our material leads us to regard acidosis, alone or with toxemia, as the major cause of fetal loss. Table IV graphically illustrates that severe acidosis carries a high fetal mortality in mild diabetes, and that any degree of acidosis is lethal in severe diabetes.

Toxemia

Reports vary as to the incidence of toxemia in diabetes, but it is consistently high. With the exception of Reis', all large series range from 24 per cent to 56 per cent. Bromberg and Toaff[17] observed rapid development of edema and fulminating pre-eclampsia in successive pregnancies, with a high fetal loss. The relationship of toxemia and diabetes has many interesting facets, which will be studied in detail in a subsequent report. Our experience may be summarized as follows:

There were 69 cases of toxemia, including two toxic separations of the placenta, an incidence of 42.6 per cent, with a fetal loss of 22 (31.9 per cent). This is fourteen times the ten-year toxemia rate recently reported[18] for this hospital. Essential hypertension appears frequently (21.7 per cent) as might be expected in a disease with a predilection for the vascular tree. As in nondiabetic women, one-third of the hypertensive patients developed superimposed pre-eclampsia. Plotting types of toxemia against age groups brings out that hypertension attacks the older women, but not necessarily the older juveniles of several years' duration. Pre-eclampsia, as usual, is indiscriminate in its selection of victims.

TABLE V. FETAL LOSS—EFFECTS OF THE COINCIDENCE OF ACIDOSIS AND TOXEMIA

	WITHOUT ACIDOSIS	WITHOUT ACIDOSIS	WITH ACIDOSIS	WITH ACIDOSIS
With toxemia				11/16 68.8%
Without toxemia			12/28 43.6%	
With toxemia		11/53 20.8%		
Without toxemia	14/65 21.5%			

Gross fetal loss of 48 (counting one pair premature twins as a unit) in 162 deliveries.

Toxemia alone has produced fetal death in some cases, and has contributed in conjunction with acidosis to others. There is so much overlapping of toxemia and acidosis, further complicated by congenital anomaly and prematurity, that it is difficult to determine their relative importance. Table V expresses fetal loss in all pregnancies. Considering only the dead infants, the loss was 28.0 per cent in the absence of toxemia, and 31.9 per cent when it was present.

The loss was only 21.2 per cent in the nonacidotic, but rose to 52.3 per cent when the mother was acidotic. This indicates that acidosis plays a more significant role in fetal mortality than does toxemia.

Hydramnios and Fetal Hydrops

The appearance of hydramnios ordinarily raises the suspicion of congenital anomaly, and this fact may act as a deterrent if cesarean section is being considered. Only 2 of our 10 cases of anomalies had hydramnios. Neither had spina bifida or meningocele, the types usually associated with hydramnios. Both had cardiac and intestinal anomalies which should have permitted survival for a short time; both were grossly hydropic; both mothers had either toxemia or acidosis; and both infants were stillborn. Of 13 cases of hydramnios, 5 of the 6 dead infants were of mothers with severe acidosis or toxemia. In fact, the most consistent finding in hydramnios was toxemia 7 times, acidosis once, and both once (70 per cent). In only 4 cases (30 per cent) was there neither toxemia nor acidosis; and only one premature infant in this group died. Ritmiller and Nicodemus[19] also noted hydramnios as a precursor of fetal death.

The correlation of hydramnios and fetal hydrops is impressive. There were 6 grossly hydropic infants. Five were with hydramnios, all in the presence of toxemia and/or acidosis, and all died. The single case of hydrops without hydramnios was in the stillborn infant of a severely acidotic mother.

Development of hydramnios suggests impending fetal hydrops; the possibility of congenital anomaly is of considerably less importance. The chances of survival of a damaged hydropic fetus are small. Prompt delivery, before the condition progresses from simple diabetic edema to frank hydrops, may effect a salvage. Perhaps until more data can be accumulated on this point, developing hydramnios may be regarded as an indication for termination of pregnancy, especially if acidosis or toxemia is present.

TABLE VI. PREMATURITY—RELATIONSHIP OF MATERNAL COMPLICATIONS TO FETAL LOSS (DIABETIC INFANTS 2 POUNDS, 2 OUNCES TO 5 POUNDS INCLUSIVE)

COMPLICATION	STILLBIRTH	LIVE BIRTHS			FETAL LOSS	
		INFANTS	DEATHS			
Acidosis alone	5	2	1	50.0%	6/7	85.7%
Toxemia alone	0	10	5	50.0%	5/10	50.0%
Both in same mother	2	1	0		2/3	66.6%
Congenital anomaly	0	0	0		0	
No evident maternal complication	2	4	4	100.0%*	6/6	100.0%
Total	9	17	10	58.8%	19/26	73.1%

*These infants weighed 2 pounds, 12 ounces, 2 pounds, 14 ounces, 3 pounds, 9 ounces, and 4 pounds, 2 ounces. One showed cerebral hemorrhage at autopsy; the cause of death in the other three was evidently the prematurity.

Prematurity

We were interested in the high incidence of prematurity in diabetes, and the substantial fetal loss which accompanies it. The maternal complications involved in premature labor are indicated in Table VI, with acidosis and toxemia outstanding. One of the arguments for hormone therapy is that it prevents premature labor. Table II demonstrates that when the figures are cor-

rected for early induced delivery, toxemia, and acidosis the incidence of spontaneous labor is not appreciably greater than in the general population. It is improbable that hormone substitution can solve this problem.

Analysis of Fetal Loss

Fetal salvage is the ultimate test of any method of treatment. Our gross fetal mortality of almost 30 per cent is much too high, but lessons can be learned by breaking it down into its component parts. Excessive preventable loss occurred from acidosis. Better management could have improved the toxemia picture. Modern nursery care would have saved some of the larger premature infants. Better selection of the type of delivery would have improved the salvage. In saying this, it must be remembered that a twenty-five-year series extends back into the early insulin era, when the role of the sodium ion in toxemia was not appreciated, and when nursery techniques were crude by present standards.

The gross fetal mortality was 48 fetal units in 162 pregnancies (29.6 per cent). Tables I to V are computed on this basis. This number includes one infant transferred to another hospital, who died following operation for intestinal atresia. It is counted as a death to compensate the statistics for congenital anomaly incompatible with life. If each of three pairs of twins is taken as an individual, there were 49 deaths among 165 infants (29.7 per cent). Table VII and subsequent charts are computed on this basis.

Of 23 infants lost before 36 weeks (Table VII) 56.5 per cent were of toxic and/or acidotic mothers. There were 3 cases of combined hydramnios and hydrops with severe toxemia; and one of hydrops in the infant of an apparently

TABLE VII. FETAL LOSS—CAUSE OF DEATH UNDER 36 WEEKS

CAUSE OF DEATH	MACERATED		STILLBORN		NEONATAL		TOTAL	
Acidosis alone	4				1		5	21.7%
Toxemia alone			1		5		6	26.1%
Mother both acidotic and toxic	1				1		2	8.7%
Congenital anomaly	1		1				2	8.7%
Prolapsed cord			1				1	4.4%
Prematurity:					4		4	17.4%
2 pounds, 12 ounces								
2 pounds, 14 ounces								
3 pounds, 9 ounces								
4 pounds, 2 ounces								
"Unexplained" intrauterine death	3						3	13.0%
Total	9	39.1%	3	13.0%	11	47.9%	23	100.0%

TABLE VIII. FETAL LOSS—CAUSE OF DEATH AT 36 WEEKS AND AFTER

CAUSE OF DEATH	MACERATED		STILLBORN		NEONATAL		TOTAL	
Acidosis, with or without toxemia	6		2				8	30.8%
Toxemia the major cause	4		1		1		6	23.1%
Congenital anomaly	1		1		2		4	15.4%
Intrauterine asphyxia, cord about neck			1				1	3.8%
Traumatic vaginal delivery			2				2	7.7%
Pulmonary edema, atelectasis					2		2	7.7%
"Unexplained" intrauterine death	3						3	11.5%
Total	14	53.9%	7	26.9%	5	19.2%	26	100.0%

normal mother. Only the 3 "unexplained" intrauterine deaths, together with 3 of the hydrops cases, might conceivably have been salvaged by hormone therapy.

There were 26 deaths at 36 weeks and later (Table VIII). Seventy-one and three-tenths per cent of the macerated infants, 43.0 per cent of the other stillborn, and 20.0 per cent of those who died in the neonatal period were infants of acidotic mothers, many of whom also had toxemia. Only 5 might have been saved by hormones. This salvage of a maximum of 11 possible infants by hormone therapy would have reduced the gross mortality from 29.7 per cent to 23.0 per cent, a not very impressive gain.

Table IX shows that about one-fourth of the fetal loss was caused by prematurity, anomalies, and accidents which can be considered inevitable. Of the remainder, 29 were associated with acidosis and/or toxemia. If just these two complications could be eliminated, the mortality would be reduced to 12.7 per cent. Better selection of delivery in two or three other cases would have put it under 10 per cent.

TABLE IX. FETAL LOSS—CAUSE OF DEATH

CAUSE OF DEATH	CASES	INCIDENCE
Prematurity, without acidosis or toxemia, under 4 pounds	3	13/49 26.9%
Congenital anomaly	6	Probably
Intrauterine asphyxia, cord about neck	1	inevitable
"Unexplained" maceration	3	
Acidosis, with or without toxemia: Under 4 pounds	7	36/49 73.1%
Acidosis, with or without toxemia: 4 pounds, 1 ounce, to 5 pounds	7	Possibly
Acidosis, with or without toxemia: Over 5 pounds	15	prevent-
Premature over 4 pounds, without toxemia or acidosis	1	able
Accidents of delivery, traumatic vaginal delivery	3	
"Unexplained" intrauterine death, over 5 pounds	3	

Time of Delivery

Many writers advocate termination of pregnancy at 36 to 38 weeks, to forestall late intrauterine death. Hurwitz and Higano[13] found a sudden upswing in the cumulative death curve from 38 per cent at 35 weeks to 81 per cent at 37 weeks. They suggest that planned delivery be moved forward to 35 weeks, but raise the logical question as to whether this would increase the loss from prematurity. Our cumulative loss gradient was more gradual (Fig. 1), and did not reach 80 per cent until after 38 weeks. Plotting fetal death by weeks (Fig. 2) shows peaks at 36 and 38-39 weeks, which are markedly diminished when loss from toxemia and acidosis is corrected for. This implication that these two complications are incriminated in the last month is brought out even more forcefully in Fig. 3, in which they are shown in relation to the entire fetal loss each week. In 4 of the last 6 weeks, either or both were the primary cause or major factors in 100 per cent of the fetal loss. All this gives an impression rather than proves anything concrete. Although Hurwitz' and this series are the largest nonhormone reports so far published, the number of deaths in any week is so small as not to be statistically significant. What does seem clear is that there is no "magic week" which can be set as a target date for delivery.

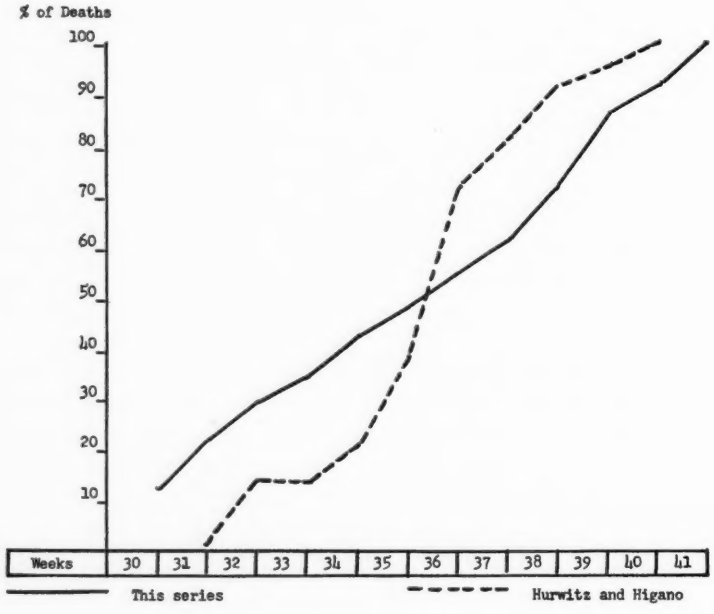
In the five-year period, 1946-1950, our uncorrected neonatal loss in all prematures between 2 pounds, 2 ounces, and 5 pounds was 20.1 per cent. In view of

this, conservatism in terms of time remains a sound policy. It is just as sensible to gain maximum possible maturity in a diabetic as in any other infant, *provided the mother is not toxic and is in good diabetic control.* When control becomes unstable, toxemia supervenes, or hydramnios develops, the fetus is in jeopardy. Pregnancy should then be promptly terminated, by cesarean section if necessary.

Cesarean Section

The problem of cesarean section has two distinct components: (1) The advocates of early delivery face the dilemma of how to accomplish this through an unprepared cervix. The answer has been a high section rate, which has raised protests against an incidence as high as 50 to 65 per cent. (2) The fetus of the diabetic who approaches term is frequently large, not to mention the increased number of breech presentations. Thus the more late deliveries, the more disproportion.

CUMULATIVE FETAL LOSS BY WEEKS.



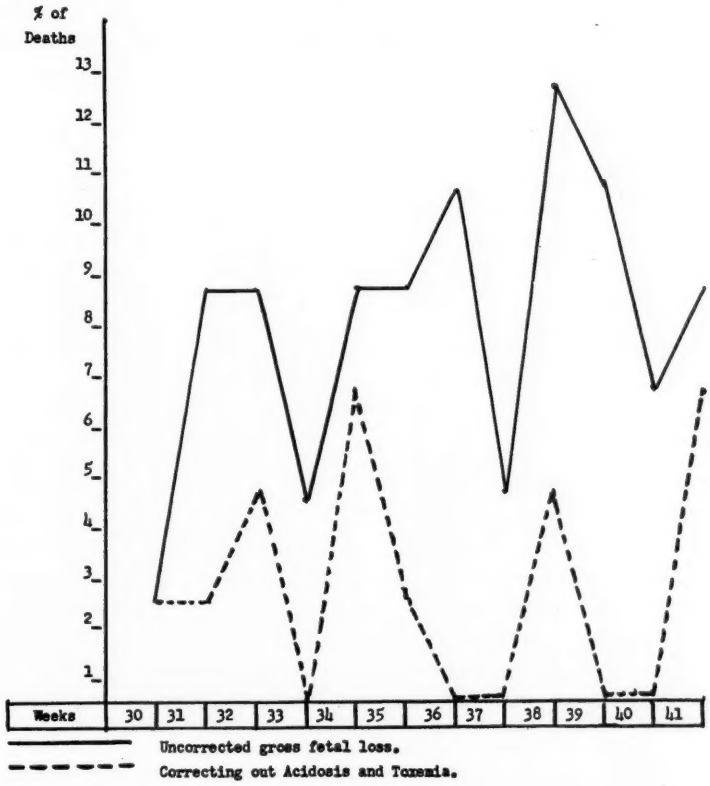
The exact time of fetal death is not always easy to determine. In allocating death by weeks, the following criteria are used: For macerated fetus time of death is week in which movement or heart sounds were lost; if not recorded, the week prior to delivery. In non-macerated stillbirths, the week of delivery. For neonatal death the week of delivery is used, regardless of how long the fetus survived thereafter.

Fig. 1.

The policy of this hospital is to section on obstetrical indications. Of 25 sections (15.4 per cent) roughly one-third were for primiparous breech, transverse presentation, and disproportion. Another third were for placenta previa, toxemia, and premature separation. In less than a third was the diabetes the

primary indication. We had 122 deliveries at 36 weeks and later, of which 103 were vaginal and 19 sections. In retrospect, earlier section should have salvaged the fetus in 2 cases of toxemia, and possibly was indicated in 2 others. Cesarean section rather than a vaginal attempt should have been done on 2 gigantic infants, and possibly on the one with prolapsed cord. This represents a section rate of 20 per cent, which would probably have paid dividends; but it is doubtful if an increase beyond this point would have materially improved fetal salvage. It is conceded, however, that if some of the deaths in utero from toxemia and acidosis had been prevented, those infants might well have presented disproportion at term, and thus would have raised the rate still further.

FETAL LOSS BY WEEKS - (Expressed in % of 49 fetal deaths.)



The corrected peak at 38 weeks consists of one congenital anomaly and one traumatic vaginal delivery. The 41 week peak includes one cord around the neck and one traumatic delivery in three cases.

Fig. 2.

The last ten-year hospital cesarean section rate was 3.8 per cent. It was four times as great in diabetes over a twenty-five-year span. This implies that the staff operated when the indications recognized as pertaining in the current era were fulfilled. The trend to cesarean section is increasing. Several factors contribute

to this: the safety of the operation today; termination of more primiparous breech and toxic pregnancies by section; and, to a lesser extent, the present doctrine of early delivery has been an influence. Inextricably tied in with the problem is the matter of the type of diabetics under observation. A clinic such as White's, with a high proportion of severe and unstable juvenile diabetics, understandably has a higher cesarean section rate than a service in which the majority of patients have mild cases or are older multiparas. As more young diabetics reach the childbearing age, there will be a rising curve of the situations which can best be resolved by cesarean section; and the repeat operations on these girls will produce a second rise. The material now seen in this hospital appears to justify a rate in the vicinity of 20 per cent. As this clientele changes in character, it is quite possible that the rate should go even higher.

FETAL LOSS BY WEEKS
(Percentage of fetal deaths in each week in which acidosis or toxemia were the primary cause or a major factor.)

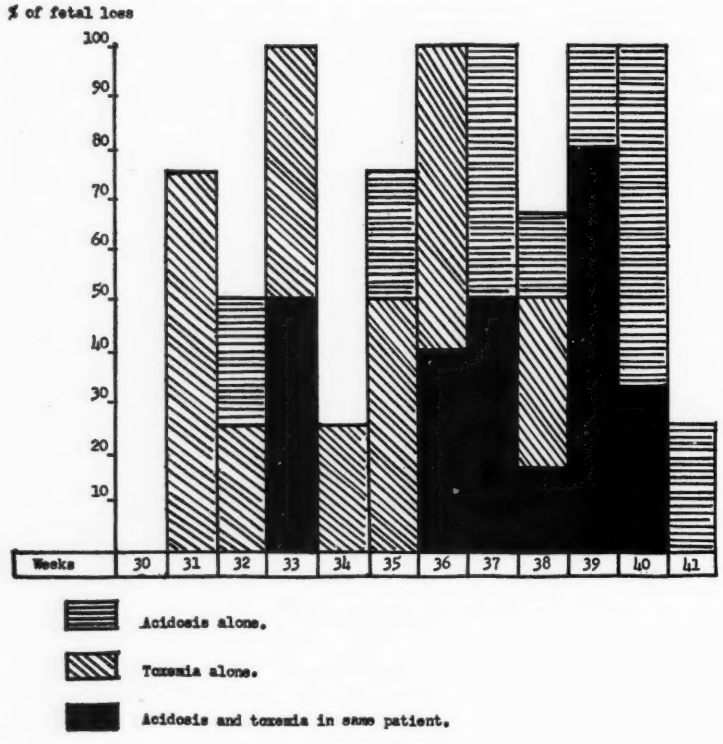


Fig. 3.

Role of Hormone Therapy

The basic concept of hormone therapy is that hormonal imbalance causes faulty nutrition and development of the diabetic placenta. This produces early senescence, resulting in premature labor and late intrauterine death. Restora-

tion of the hormone balance by substitution therapy is supposed to prevent this senescence, and is also presumed to prevent toxemia. This is an attractive theory, but it lacks confirmation. Reis[10] enumerates the theoretical objections. From the practical standpoint, this can be said:

1. The "senescent placenta" has not been demonstrated, clinically or pathologically, to be a recognizable entity which accompanies the complications of diabetes with any regularity.

2. The evidence seems to be against such a placenta causing intrauterine death per se. Of 26 deaths at 36 weeks and later, only 3 could not be adequately explained by acidosis, toxemia, congenital anomaly, or accidents of delivery. The close correlation with acidosis and toxemia is too striking to be a mere coincidence. It is not necessary to ascribe death to some intangible placental abnormality, except in rare instances.

3. As previously remarked, it is improbable that the use of hormones can materially reduce the onset of spontaneous premature labor in uncomplicated cases.

4. It can be readily demonstrated that hormone therapy has not reduced toxemia in diabetes. White's[20] incidence in 439 cases was 44 per cent. The incidence in the small combined hormone series of Palmer,[6] Randall,[8] Hurwitz,[13] and Rike[15] comes to 43 per cent. The nonhormone cases of Reis,[10] Given,[11] Hall,[12] Hurwitz,[13] and this paper is a combined total of 566 pregnancies with a toxemia incidence of 37 per cent. If anything can be made of this scant margin of advantage, it is to emphasize the objection that stilbestrol enhances the retention of sodium and water, and so may invite toxemia.

5. The practical disadvantages of the White regime are obvious. The expense of medication puts it beyond the reach of clinic and many middle-class patients. The hormone titers require laboratory facilities available to few obstetricians. The substitute use of oral stilbestrol is a short cut which both White[20] and Keltz and his co-workers[21] found to be relatively ineffective.

We do not reject hormone therapy in toto. It must be conceded that White has had remarkable results in the types which universally give trouble: the women with long-standing diabetes, in whom there are established vascular and renal changes. Our experience coincides with that of others in that the incidence of acidosis, toxemia, and fetal loss are highest in the older juveniles, in the ten-year diabetics, and in women over thirty regardless of when their diabetes was acquired. If hormone therapy has any merit it should be in such selected cases. It would be appropriate to offer it as an adjunct to orthodox care, if the patient can afford it and if the laboratory facilities are available to do it properly. Even a small fetal salvage is worth while in these women.

Conclusions

In 25 years 184 diabetic pregnancies were observed. One hundred sixty-two of these reached viability with no hormone therapy. From this study it is concluded:

1. The most important causes of fetal loss are acidosis and toxemia. The management of the pregnant diabetic patient is a threefold responsibility:

(a) Good obstetrical judgment, aimed particularly at control of toxemia and at selection of the safest method of delivery. (b) Experienced and constant medical supervision directed at prevention of acidosis. (c) Modern pediatric care of the edematous infants and the prematures. Under these conditions the fetal loss should approximate 10 per cent without the use of hormones.

2. Hormone therapy offers little in mild and uncomplicated cases of diabetes. If the method has value, it should be employed in the older juveniles, the ten-year diabetics, and the older women.

3. There is no optimal point in weeks at which to terminate pregnancy, nor is there any clear-cut advantage in routine early delivery at any arbitrary time. Intervention should be predicated on deteriorating control of the diabetes, threatening toxemia, or the appearance of hydramnios.

4. The indication for cesarean section should be obstetrical in the broad sense. The necessity for early intervention for acidosis or toxemia, the increased size of the infants, and the high incidence of malpositions will combine to create a cesarean section rate higher for diabetic patients than for the general population. The proportion of juvenile diabetics will also influence this rate. At present the material seen in our clinic warrants a section rate of approximately 20 per cent.

Note.—Since this paper was prepared for publication, Pedowitz and Shlevin have reported a series of 156 viable pregnancies without hormone therapy. Their findings are comparable, particularly as to the role of acidosis and toxemia (Bull. New York Acad. Med. **28**: 440, 1952).

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WHAT IS THE STATUS OF THERAPEUTIC ABORTION IN MODERN OBSTETRICS?*

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THE two great purposes of the art of medicine are to save life and to relieve suffering. Any situation wherein a physician not only witnesses death but is called upon to cause it must be doubly distasteful to him. A therapeutic abortion is such a situation. It is really an admission of failure on all parts to control disease and remove its threat to the life of the mother." Thus did Bowles and Domzalski[1] in 1949 summarize one of the most important and controversial problems in modern medicine—important because therapeutic abortion is identified with a plan, however well intentioned, which culminates in the deliberate destruction of the fetus prior to the period of viability; controversial because in this one phase of medicine the life of the baby is unconditionally surrendered to the disease of the mother. The physician from earliest times has dedicated his life to the *saving* of human life. Leaders in our profession from the days of Hippocrates have emphasized this concept and have particularly stressed the responsibility of the physician in safeguarding the life of the unborn child. As recently as 1948, one of the most important precepts propounded by the World Health Organization in its Declaration of Geneva is the statement, "I will maintain the utmost respect for human life from the time of conception; even under threat I will not use my medical knowledge contrary to the laws of humanity."

Therapeutic abortion is, therefore, a direct violation of the fundamental ideals and traditions of medical practice. It is distressing to find that it has received scant attention in obstetrical literature, whereas authorities in the appropriate specialties concerned with the complications of pregnancy have been most articulate during the past twenty-five years in condemning abortion as a therapeutic measure. They have repeatedly emphasized that, as far as a complicating disease is concerned, the expectant mother presents a problem not greatly different from that of a nonpregnant sister with the same disease, and that furthermore, so far as her pregnancy is concerned, she is not greatly different from other pregnant women.

Despite such testimony, it has been estimated that over 18,000 therapeutic abortions are performed each year in the United States. In the face of such appalling loss of life, one is forced to the conclusion that therapeutic abortion has been seriously neglected in obstetrical literature, and is very probably the most poorly regulated procedure in medicine.

*Presented at a combined meeting of the Boston, New York, and Philadelphia Obstetrical Societies, Boston, April 21, 1953.

To secure definite factual information, questionnaires were sent to 367 hospitals in this country. Replies were received from 171, of which 152 supplied detailed information as requested (Table I). These hospitals were selected (a) because they have been approved for the training of residents or interns; (b) because of their diversified geographical location, and (c) because of the number of deliveries. It was felt that information from such institutions would be accurate and that the cases reported would have been adequately studied.

TABLE I. GENERAL ANALYSIS OF QUESTIONNAIRES

Number of questionnaires sent out	367		
Number of questionnaires returned	171		
Number of hospitals where therapeutic abortions were done		79	
With sufficient data for analysis			69
Number of hospitals where therapeutic abortions were not done		92	
With sufficient data for analysis			83
Total number of hospitals whose replies were adequate for study			152

The study was divided into two five-year periods, 1941-1945 and 1946-1950. The total number of deliveries involved in the study was over three million, a figure which becomes important when it is realized that this approximates the number of deliveries in the entire nation in one given year. The death rates per 1,000 (Table II) shown in the two series testify to the good obstetrics performed in these institutions, inasmuch as a maternal mortality rate of less than 1 per 1,000 was not achieved by the nation as a whole until 1950. Of special interest is the fact that the maternal mortality rates in the hospitals performing therapeutic abortions, while excellent, were not better than those in the hospitals wherein no therapeutic abortions were performed. In fact, a few more mothers died in the hospitals allowing therapeutic abortions. It may not be argued that those hospitals allowing therapeutic abortions necessarily fell heir to a greater number of complicated obstetrical cases. The hospitals in both groups, in direct answer to a specific question, replied that they did not refuse admission to any patients except those suffering from communicable disease. In not a few instances the hospitals which replied to our questionnaire represented the only major or teaching unit in a large area; in some cases they permitted and in others they forbade therapeutic abortions. It is reasonable to assume that in some instances patients were not accepted for admission where therapeutic abortion was the *announced purpose* for hospitalization. As will be pointed out later, the proper control of therapeutic abortion can be maintained only under the impersonal and objective atmosphere of hospital practice.

TABLE II. MATERNAL MORTALITY

	NO THERAPEUTIC ABORTIONS			THERAPEUTIC ABORTIONS		
YEARS	DEATHS	DELIVERIES	RATE/1,000	DEATHS	DELIVERIES	RATE/1,000
1941-1945	827	642,788	1.28	971	599,685	1.61
1946-1950	642	1,038,201	0.61	587	975,032	0.61
Total	1,469	1,680,989	0.87	1,558	1,574,717	0.98
		Totals Both Groups, Both Periods				
	3,027	3,255,706			Rate - 0.93	

The breakdown of the causes of maternal mortality (Table III) shows a striking parallelism in the two groups. Hemorrhage, shock, and toxemia are the big killers as might be expected in any obstetrical survey. It is surprising to see pulmonary embolus so high on the list and disturbing to notice such an uninstructive term as "cardiac failure" so prominent. Ruptured uteri and anesthesia again testify to the high incidence of man-made causes of maternal mortality even in the best circles. The only real disparities in the two groups are found in tuberculosis and criminal abortion. In each instance an unusually large contribution from a single hospital influenced the figures. This table represents a continuing argument for strong, well-regulated obstetrical departments in all hospitals and demonstrates again how many maternal deaths are still preventable. This information will be fruitful only in so far as it can stimulate renewed efforts toward better cooperative prenatal care and education of physicians and the public alike.

TABLE III. CAUSES OF MATERNAL MORTALITY

NO THERAPEUTIC ABORTION DONE		THERAPEUTIC ABORTION DONE	
1. Eclampsia, toxemia	244	1. Eclampsia, toxemia	270
2. Hemorrhage, shock	244	2. Hemorrhage, shock	164
3. Pulmonary embolus	126	3. Pulmonary embolus	117
4. Cerebral accident, hypertension, nephritis	98	4. Cerebral accident, hypertension, nephritis	104
5. Cardiac failure	70	5. Cardiac failure	86
6. Ruptured uterus	45	6. Infection	66
7. Infection	39	7. Criminal abortion	61
8. Abruptio placentae	38	8. Ruptured uterus	47
9. Rheumatic heart disease	36	9. Anesthesia	41
10. Anesthesia	28	10. Abruptio placentae	38
11. Pneumonia	24	11. Rheumatic heart disease	37
12. Placenta previa	23	12. Peritonitis	34
13. Tuberculosis	6	13. Tuberculosis	33
14. Criminal abortion	3	14. Pneumonia	28
		15. Placenta previa	27

The total number of therapeutic abortions done, as shown in Table IV, was 2,717 with a rate of 2.3 per 1,000. The wide variation in rate, 0.2 per 1,000 and 7.3 per 1,000 over this ten-year period, points to a disunity of opinion as to their necessity or a marked variation in the indications. In this series, the incidence represented a ratio of 1 in 418 deliveries. That this is low is attested by the statement of Eastman[2] who estimated a ratio of 1 in 150 to 1 in 200 deliveries, and that of Tietze[3] who in a five-year period in New York City found it to be 1 in 213 deliveries. It is worthy of comment

TABLE IV. GENERAL FREQUENCY OF THERAPEUTIC ABORTION IN THIS AND OTHER REPORTED SERIES

Total number therapeutic abortions	2,717
Total number deliveries during same period in hospitals supplying adequate statistics	1,135,618
Rate per 1,000 births	2.38
Variation in rate per 1,000 births during 10 year period	0.2/1,000 to 7.3/1,000
Ratio to deliveries	1 in 418
Eastman[2]	1 in 150 to 1 in 200
Tietze[3]	1 in 213

to point out that the latter author noted the ratio in New York City to be eight times as frequent in private patients as to service cases.

The incidence of therapeutic abortion per 1,000 deliveries in sixteen university level hospitals is shown in Table V. These were all secular institutions. Three of these hospitals allowed no therapeutic abortions. The others vary in their incidence from 0.43 to 8.55 per 1,000. The trend, with one exception, is toward a lessened destruction of fetal life. It is worthy of comment that five other hospitals of university level either had *no statistics available* or had not compiled them on this important subject.

TABLE V. INCIDENCE OF THERAPEUTIC ABORTION PER 1,000 DELIVERIES IN SIXTEEN UNIVERSITY LEVEL HOSPITALS

HOSPITAL	1941-1945	1946-1950
1	0	0
2	0	0
3	0	0
4	*	0.58
5	1.04	0.48
6	1.29	0.60
7	1.32	0.81
8	1.34	0.43
9	1.38	2.64
10	4.16	3.01
11	—	3.58†
12	5.3	3.9
13	6.61	4.50
14	7.44	7.15
15	7.5	5.3
16	8.55	6.95
Number of hospitals where statistics not available or not compiled, 5.		

*No statistics available for this five-year period.
†Rate for ten-year period, no five-year rate given.

The indications for therapeutic abortion in this series have been broken down into four groups. The first group (Table VI) represents those disease entities whose successful management in pregnancy depends on good prenatal care. Chief on the list of these is tuberculosis. The tremendous weight of opinion opposing this may be summed up in the denunciation of the interruption of pregnancy presented by Jacobs[4] in 1946, who after analyzing the literature for thirty years said, "If abortion is to have any scientific justification, evidence must be sought showing that in general the harmful effects are avoided if the pregnancy is being interrupted. A study of the literature will soon convince any impartial person that no such evidence exists."

TABLE VI. INDICATIONS FOR THERAPEUTIC ABORTION
I. Complications Subject to Prenatal Care Control

Tuberculosis	260
"Cardiac"	240
Rheumatic heart disease	173
Congenital	7
Pre-eclampsia	120
Fibroids	72
Hyperemesis	46
Diabetes	19
Total	937

Opinions of many eminent cardiologists[5-9] through the years support the contention that heart disease in pregnancy can be successfully managed by competent prenatal care. Thus, Gorenberg[10] states, "It is probable that practically every pregnancy encountered in a patient with heart disease can be brought to a successful spontaneous termination if adequate prenatal care is instituted and if absolute bed rest is enforced when indicated." One hundred twenty pregnancies were interrupted for pre-eclampsia before viability. If, indeed, by modern definition, these represented true pre-eclampsia rather than cardio-vascular-renal disease, good prenatal care could have saved most of these lives.

Although fibroids can add to the obstetrician's worries, surely no pregnancy should be interrupted for this benign condition.

Present-day management should eliminate hyperemesis and diabetes from any discussion of therapeutic abortion.

The second group of indications for therapeutic abortion (Table VII) may be classified as complications arising from metabolic, degenerative, or infectious diseases.

TABLE VII. INDICATIONS FOR THERAPEUTIC ABORTION

II. Complications Associated With Metabolic, Degenerative or Infectious Processes

Chronic nephritis, hypertension, cardiovascular	282
"Medical"	97
Rh problems	26
Cancer of breast	17
Rubella	26
Total	448

Chronic nephritis, hypertension, and cardiovascular disease may offer serious problems. Many authorities have claimed that in nephritic patients the greatest danger to the mother is represented by further renal damage with each successive pregnancy. Reid and Teel[11] and Dodds and Browne[12] found that this was not true in over 50 per cent of their cases. The latter authors stated that they "were unable to ascertain that the worsened renal status in the other patients was induced solely by the pregnancy rather than by the usual downhill course of the glomerulonephritis itself." Among the hypertensive patients, those who do not spontaneously abort may be managed by conservative methods including sympathectomy when indicated. Newell and Smithwick,[13] in reporting 14 cases of pregnancy following lumbodorsal splanchnicectomy, conclude: "Following a satisfactory response to operation, pregnancy, if carefully supervised, appears to be safe and permissible. The experiences presented above lead us to believe that following this operation certain hypertensive women may be able to tolerate pregnancy, which would be otherwise impossible or extremely hazardous. This is particularly true in the younger age group with severe essential and even malignant hypertension."

The only indication given in 97 cases was "medical." This again demonstrates the almost casual attention given in some institutions (and necessarily by the department heads as well as by the attending physicians) to an opera-

tion which, regardless of the purpose to which it may be dedicated, per se destroys life.

The Rh factor has produced its share of abnormal children. However, the positive constructive approach (not the destructive approach of therapeutic abortion) to the problem has salvaged a gratifying number by the exchange transfusion. The physician who has seen mothers develop rising titers in the last trimester and then deliver normal babies will not be trapped into doing therapeutic abortion. Rising titers and other danger signals will stimulate him to prepare for an exchange transfusion in an effort to save the baby.

The difficulties arising from the Rh factor have emphasized a new aspect of therapeutic abortion which has been carried over, as will be seen, to the situation found in rubella in pregnancy. In such cases, therapeutic abortion is being recommended in the *absence of a threat* to the mother's health and life and merely in the face of a *possibility* that the child would be born defective. Such therapeutic abortions are illegal, even in many states where the operation is "legalized," and from a medical point of view they must be condemned since they assume untenable predictions to be facts. They are destructive in their approach, and are separated, by the mere width of the uterine wall, from the concept that defective children and the incurably ill should be sacrificed "for the good of the community."

Carcinoma of the breast in pregnancy presents, many times, a tragic impasse replete with medical, emotional, and socioeconomic problems. It has been considered a "legitimate" reason for therapeutic abortion. Eastman,[14] in commenting on a paper by Morton on "Malignancy and Pregnancy," states: "Of particular interest and importance is the author's statement about mammary cancer and pregnancy, namely, that therapeutic abortion does not increase the chances of cure. I believe that Morton is correct in his contention but, as he well knows, the consensus around the country is just the reverse, especially among surgeons, who almost invariably urge therapeutic abortion in all such cases."

Westberg,[15] in the most exhaustive work on the subject to date, concludes: "Nothing has been found to bear out the opinion that induced abortion should improve the prognosis. Nor does the prognosis seem to depend on the fact whether or not the patient nurses her offspring. It would thus seem that the pregnancy has no very great effect on the prognosis of breast cancer apart from the fact of the patient's delay in consulting a doctor and the doctor's inclination to postpone surgery."

Since the work of Gregg[16] in 1941, who found congenital defects in almost 100 per cent of the babies delivered by mothers who had rubella early in pregnancy, subsequent reports have shown a progressively lower incidence.

"There is a definite danger," says Tenney,[17] "in the assumption that the patient who has rubella in the early weeks of gestation should have the pregnancy terminated. The diagnosis of rubella is sufficiently vague to be easily abused. In addition, many healthy children are born from mothers who have

had rubella. Other virus diseases may affect the infant, but we cannot assume that these are indications for abortion." The editors of the *New England Journal of Medicine,*[18] in making a plea for data on such cases state, " . . . Yet, even ten years after the teratogenic capacities of the virus have been established, the precise risk cannot be stated—so rare are cases among adult females at a selected stage of gestation, so variable are the expressions of maternal infection in the infant, so cumbersome is the task of case finding, follow-up study, classification of defect and centralization of data. It is doubtful, however, that the risk of serious malformation is more than 15 per cent even at the first, crucial trimester of pregnancy, and it may prove less. . . . No physician is justified in stating categorically that rubella in the first trimester of pregnancy is always associated with a bad prognosis."

As an indication for therapeutic abortion, neuropsychiatric diseases (Table VIII) have been greatly abused. Arbuse and Schechtman[19] have an excellent critical review of this subject. They state, "There does not seem to be any one condition which absolutely indicates interruption of pregnancy." Ebaugh and Heuser[20] are of the opinion that the interruption of pregnancy may do far more harm than good to a person with a well-balanced nervous system and may cause considerable damage to the patient with a psychiatric difficulty. They state, "These changes coupled with ideas of guilt, self-deprecation, some recurrent preoccupation centering around the abortion and the general theme of 'I let them kill my baby' might well disturb a poorly integrated personality even to psychotic proportions. Feelings of love, admiration and respect for the male partner in the result of pregnancy may well be distorted in the aborted woman to ideas of disgust, hate, and disrespect; 'He gave gave me a baby, then took it away.' The unconscious motivation and the even flow of emotions during the readjustments to a normal sexual nonpregnant cycle may result in deeply engrained feelings of hostility toward the husband. Abortions we may say can produce psychologic cicatrix."

TABLE VIII. INDICATIONS FOR THERAPEUTIC ABORTION
III. Complications Neuropsychiatric

Psychoses	331
Neurosis	46
Epilepsy	16
Multiple sclerosis	11
Total	404

Epilepsy, as one of the classic diseases of history, has been the subject of much superstition and misapplication of data. It is not surprising that it be urged as an indication for therapeutic abortion. However, since its "hereditary" stigma has been largely discredited, there remains only the consideration of the possible mutual effects of pregnancy and the disease.

Burnett[21] has written an excellent summary of the situation and he finds that most writers agree with Greenhill that epilepsy has usually no effect on pregnancy. As to the effect of pregnancy on epilepsy, he states:

"Probably Rubeska is as near the truth as anybody when he considers that one-third of the cases improve, one-third become worse, and one-third remain unchanged. . . . We must agree with Sachs that when pregnancy occurs in an epileptic mother it has an influence on the disease which is completely unpredictable."

Multiple sclerosis is an unhappy disease which when combined with pregnancy may present a problem in management and so has been a target for therapeutic abortion. The disease may be extremely difficult to diagnose. It is characterized by remissions and exacerbations of symptoms and its treatment is nonspecific. It *can* be argued that the patient with multiple sclerosis may have a remission during pregnancy with as much likelihood as that she may have an exacerbation. It *cannot* be argued validly that pregnancy is the cause of either a remission or an exacerbation since these features are almost pathognomonic of the process itself.

The chief argument proposed for therapeutic abortion in these cases is to avoid a "stress situation." As Baker[22] has put it, these patients should avoid injuries, infections, pregnancy, undernutrition, chilling, and exposure. Admittedly this may be desirable, but certainly a therapeutic abortion can increase the "stress" by frustration of motherhood, development of guilt complexes, and the ever-present danger of infection.

Furthermore, on the constructive side, these patients can and do manage pregnancy very competently. McElin and Horton[23] investigated the effect of histamine on 15 patients with neurological disease who were pregnant. Twelve of these patients had multiple sclerosis. They suffered no complications. They all delivered normally, had normal children, and six of them nursed their infants. These patients were treated, not aborted. It is submitted that such an attitude is in keeping with the proper ideals of the profession.

TABLE IX. BIZARRE INDICATIONS

"Congenital hip"		Adhesions of uterus	
Anencephaly		Court order	
Pyelitis		Uterine prolapse	
Secondary anemia		Old ununited fracture of leg	
Possible malignancy		Hypotension and anemia	
Arthritis		Obesity	
Congenital syphilis		Severe erosion of cervix	
Recent nephrectomy for stones		Pertussis	
Rape		"None Given"	6
		"Miscellaneous"	55
	Total	94	

In Table IX are listed indications for therapeutic abortion which are so astounding that they may be properly listed only as "bizarre." It is incredible that a teaching, approved institution or a department head could tolerate a situation wherein a therapeutic abortion would be done—and no indication be listed on the chart. The term "miscellaneous" as such is not objectionable, rather, the thought that after the too-long list of indications already shown in Tables VI–IX there would be so many other indications

that several record-room librarians were forced to list them together as miscellaneous. Obviously, the babies destroyed under the headings listed in this table died, not because of a medical emergency in the mother, but as a matter of convenience. It has been said that the border line between criminal and therapeutic abortion is a fine one. This table raises the question, "In cases like these is there really any difference?"

Medicine has made great progress through its self-instituted controls. The supervision which the profession, as indicated by the practice of these representative, approved teaching institutions, has exercised over therapeutic abortion is shown in Table X. Worthy of special comment are the facts that no record of consultations was compiled in eight hospitals and thirty-two hospitals did not require an obstetrician as a consultant.

TABLE X. CONTROL OF THERAPEUTIC ABORTION

Number of hospitals not compiling any record	8
Number of consultants required (av.)	2.5
Number requiring only one consultant	12
Number not requiring an obstetrician as one of the consultants	32
Number requiring "anyone," i.e., "staff member," member State Medical Society, etc.	2
Number requiring consultants to be chiefs of services	3
Number requiring unanimous vote of consulting committee	4
Number of hospitals requiring each case to be presented anonymously	12

Summary and Conclusions

As therapeutic abortion involves the direct destruction of human life, it is contrary to all the rules and traditions of good medical practice. From the very beginning, the approach to the problem has been unscientific. In too many cases it was learned, after innumerable babies had been sacrificed, that interruption of the pregnancy not only caused 100 per cent fetal loss but also increased the maternal mortality. The sad history of the use of therapeutic abortion in pneumonia,[24] cardiac decompensation,[25] myasthenia gravis,[26] and influenza[27] shows but a few glaring examples of this false reasoning.

With such a background, what is the status of therapeutic abortion in modern obstetrics? Questionnaires sent to many representative teaching obstetrical clinics have yielded the following significant information:

1. The incidence of therapeutic abortion is disturbingly high.

2. A careful analysis of the indications for these operations makes it rather clear that with better prenatal care the lives of most of these infants could have been saved without necessarily increasing the maternal mortality.

3. The marked variation in rate in the incidence of therapeutic abortion throughout this country demonstrates the lack of unified opinion in these representative teaching centers.

4. The management of this important procedure has been uncritical and unscientific as evidenced by:

A. The unstandardized and haphazard control reported by the various hospitals.

B. The fact that some of these teaching institutions actually have neglected to compile statistics on therapeutic abortion for departmental or annual reports.

C. The apparent lack of interest on the part of examining authorities with regard to therapeutic abortion as compared to other obstetrical procedures such as the indications for and incidence of cesarean sections.

5. The maternal mortality statistics in two almost equally large and comparable series totaling over three million deliveries indicate no increased number of maternal deaths in hospitals, in which, as a matter of policy, no therapeutic abortions were performed.

When the writings of interested specialists in allied fields are analyzed,[28-46] grave doubts must arise concerning the validity of any of the listed indications for therapeutic abortion. Furthermore, many authorities have deplored the destruction of the fetus in certain complications where therapeutic abortion was performed not so much because the condition endangered the mother's life but because of the expense and social hazards involved. The death of the fetus in these cases is rationalized on a medical basis; but actually the chief motive is the socioeconomic factor. In such cases the physician not only neglects to safeguard the unborn life entrusted to his care but actually becomes the deliberate executioner of an innocent human being. Surely, this is unethical and unscientific.

One of the most serious implications of this whole question is concerned with the training of the physician of tomorrow. This survey demonstrates that in at least seventy-nine teaching obstetrical clinics, the young doctor is taught, in effect, that in a not inconsiderable number of cases, no amount of prenatal care, no recourse, however great, to the armamentarium of modern medicine will avail him in obtaining the objectives of a live and well mother and baby. In effect, he is being taught that in 1 out of 418 obstetrical cases "to heal the mother you must kill the baby."

No procedure which of its very nature violates the basic law of medicine "to preserve life" and thereby carries with it such far-reaching implications should be perpetuated in the face of grave doubts as to its necessity and when its validity lacks scientific support.

The time has come for the profession to accept, affirm, and teach the rationalism in obstetrics so eloquently championed by Cooke, Cosgrove, and others. This rationalism includes "the principle that medical and surgical complications of pregnancy should be appropriately medically and surgically treated, without interference with pregnancy. It does not embrace, on the one hand, blind confidence that pregnancy is and will remain physiologic, or, on the other, a baseless fear that pregnancy may not be successfully managed in the presence of almost any complication. Intelligent improvement in obstetric practice will be principally predicated on thoughtful individualization of cases on the basis of such rationalism."[47]

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A SUGGESTED TREATMENT FOR INVERTED NIPPLES

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ALTHOUGH during the last ten years there has seemed to be a gradual turning away from breast feeding, due perhaps to the intricacies of our present-day society, there is still a large group of women who seriously desire and plan to nurse their babies. For the most part these patients do very well, with the exception of an occasional cracked nipple, which can prove to be most distressing for a period of time. Breast abscess still sometimes proves to be a disturbing complication with patients who breast feed. With careful instruction, however, as to proper breast care this complication should be avoided. One of the main difficulties with proper breast feeding today is the so-called flat or inverted nipple. If this abnormality is not corrected or at least an attempt made at correction before breast feeding begins, the procedure is usually not satisfactory nor successful. Sometimes a breast pump is used to exert considerable suction upon the nipple as a whole to withdraw it from its inverted position and, after this process has been carried out for a period of time, the child is allowed to go to the breast directly.

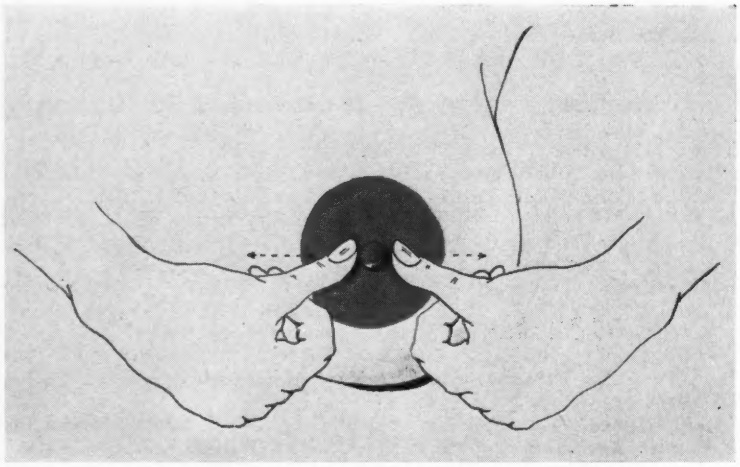

Fig. 1.—Horizontal position.

When one consults the usual texts in obstetrics, it is impossible to find specific means of therapy for this condition. In the tenth edition of *Williams Obstetrics,* Eastman[1] states, "In the presence of this anomaly daily attempts should be made during the last few months of pregnancy to draw the nipple out by traction with the fingers. This, however, is rarely successful so that if the

nipples cannot be made available by the temporary use of an electric pump, suckling will have to be discontinued." Greenhill[2] likewise has little to offer for this difficulty. He states, "If the nipples are flat, they may be drawn out for a few minutes each day during the last few weeks of pregnancy. This must be done most gently and only after demonstration by a physician or a nurse." It has been my impression that the lay journals have done a better job in describing this difficulty and its treatment than we have in our authoritative texts.

For the last two years I have been carrying out a procedure which is unusually simple to do and so far has proved to be quite rewarding with those patients who have inverted nipples and who desire to breast feed. Since beginning this type of instruction no patient has had to stop breast feeding because of this difficulty. The accompanying two diagrams portray the procedure which I have been following. The procedure is one of placing the thumbs, or the forefingers, close to the inverted nipple, then pressing into the breast tissue quite firmly and gradually pushing the fingers away from the areola. An imaginary cross is drawn on the breast, that is, a vertical line and a horizontal line, and the patient is instructed to put her two thumbs close to the nipple, press in firmly against the breast tissue, and then pull the thumb or finger laterally in the horizontal position or upward and downward in the

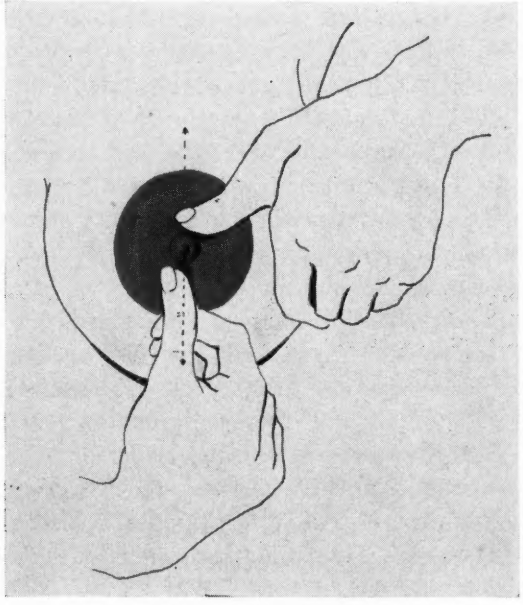

Fig. 2.—Vertical position.

vertical position. If she does this procedure four or five times in succession when she awakens in the morning, the nipple will immediately assume an erect and projected position. After it has been brought out to this projected position, it is easier to grasp as a whole unit and, by grasping it at its base, she can gently tease it out a bit further.

The patient is instructed to begin these exercises at about the fifth or sixth month of pregnancy. I have had some patients carry them out from the beginning with excellent results.

I offer these suggestions for this minor difficulty hoping that others may be willing to try this simple procedure and perhaps get the same gratifying results which have come to me.

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ACCIDENTAL PERFORATION OF THE UTERUS

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ONE of the most common operations performed by the gynecologist is diagnostic or therapeutic curettement of the uterus. Though usually a simple, safe procedure, perforation of the organ may occur with possible serious consequences. A decision must be made whether to perform an immediate laparotomy and possibly sacrifice the uterus or merely to employ expectant therapy, awaiting evidence of intrapelvic or intra-abdominal trauma with possible grave results. A search of the literature is of little aid. There are innumerable reports of the gruesome and mutilating results of this accident in operations performed by the criminal abortionist. There is, however, a paucity of references to its management when it occurs in the hands of the ethical physician, performing the operation for legitimate indications in the favorable environment of the hospital operating room. Curtis[1] states that laparotomy is indicated only in those rare instances in which the curette is manipulated after having passed through the uterine wall. Titus[2] believed that smaller perforations could be treated by lightly packing the uterus with narrow strips of gauze but that larger perforations and those occurring in the septic uterus should be treated by laparotomy, with drainage in the latter. Hessert,[3] in 1905, outlined a plan of management in these cases but advances in therapeutic methods make this no longer valid. Taussig[4] in his exhaustive presentation on abortions has reviewed the opinions of numerous authors when the operation is performed to terminate pregnancy or for incomplete abortions and points out the varying methods of management which are advocated. Murray and Winkelstein[5] have recently reported on the course and management of 27 cases of uterine perforation in the patient with abortion. Most of their cases (24) were the result of instrumentation prior to admission to the hospital. They therefore favor a somewhat radical management of this complication.

It is the purpose of this presentation to review the accidental perforations of the uterus which occurred at Bellevue Hospital between June 1, 1936 and May 31, 1952. This period represents an era in which first the sulfonamides and later the antibiotics became available in the treatment of these patients.

During the period studied there were 10,105 curettements performed for all indications. There were 51 accidental perforations in these patients, an incidence of 0.5 per cent, or approximately one perforation in each 200 operations. Table I shows the indications for the operation in those patients in which perforation resulted. It is noteworthy that no perforation occurred in patients subjected to therapeutic abortion although there were 170 of these performed.

TABLE I. INDICATIONS FOR CURETTAGE

INDICATION	NUMBER OF CASES
1. Incomplete abortion and retained secundines	16
2. Diagnostic curettage	33
3. Hydatidiform mole	2
Total	51

Table II lists the instruments which perforated the uterus. In over half the patients a sharp curette was passed through the uterine wall. A uterine sound was reponsible for the perforation in most of the remaining cases. While in this series there has been a tendency to be more radical in the treatment of patients in whom the uterus was perforated with a sharp curette, figures will be shown demonstrating that the dangers attendant on perforation by this instrument are probably exaggerated.

TABLE II. METHOD OF PERFORATION

INSTRUMENT	NUMBER OF CASES
1. Sharp curette	29
2. Uterine sound	18
3. Cervical dilators	2
4. Ovum forceps	1
5. Unknown	1

One of the more difficult factors to evaluate is the possibility of introducing infection and infected material into the peritoneal cavity, particularly in those patients with incomplete abortions. That many of these abortions are induced prior to admission to the hospital cannot be denied, but it is almost impossible to estimate the total percentage accurately. The clinical picture in the induced abortion is inconsistent. Frequently those appearing most innocent confess to some form of instrumentation, while those whose findings most strongly suggest intervention vehemently deny such a possibility. There has been a tendency through the years to be somewhat more active in the management of perforations when they occurred in the presence of an incomplete abortion. A review of the results would indicate that a more conservative approach might be utilized to advantage. These patients were most frequently subjected to laparotomy and repair of the perforation on the assumption that a fertile lodging existed for microorganisms and spillage of this material through the uterine wound would make possible a resulting peritonitis. Table III shows the morbidity incidence in 16 patients in this group treated by various methods. Twelve of these patients were subjected to laparotomy and repair of the perforation and one to hysterectomy. Until the introduction of antibiotics all of these patients were morbid. Morbidity was greatly reduced by the use of these drugs. Morbidity in those patients subjected to laparotomy is defined as a fever over 100° F. which persists for more than 72 hours following operation. In the three patients in this group treated conservatively there was no morbidity regardless of the use of antibiotics. Morbidity in these patients was defined as fever over 100° F. for more than the first 24 postoperative hours. The shorter duration was used in this group because of the lesser severity of the surgery. This would seem to

indicate that morbidity was more the result of surgery than the perforated uterus, although strong support is lacking in view of the small number of cases treated conservatively. Only one of these patients showed clinical and bacteriological evidence of infection prior to curettement and following perforation she showed evidence of peritonitis and intra-abdominal hemorrhage and a hysterectomy was performed. There was a large amount of clotted blood in the abdomen. The patient later admitted to instrumentation prior to admission and it is not unlikely that perforation occurred at that time.

TABLE III. MORBIDITY IN INCOMPLETE ABORTIONS AND RETAINED SECUNDINES

METHOD OF TREATMENT	NUMBER OF CASES	MORBID		NONMORBID	
		NO ANTIBIOTICS	ANTIBIOTICS	NO ANTIBIOTICS	ANTIBIOTICS
1. Conservative	3	0	0	1	2
2. Operative	13	4	2	0	7

On 33 occasions this accident occurred during diagnostic curettement (Table IV). As these cases are considered "clean," a more conservative approach to their management has been adopted. A study of the morbidity in these patients tends to bear out the findings in the first group. Morbidity was much higher in the patients subjected to laparotomy. Those patients treated conservatively were about 85 per cent nonmorbid. Two hysterectomies were performed following perforations during diagnostic curettement. In one patient the operation had been planned because of uterine fibroids; the other developed peritonitis, the removed uterus showing a purulent endometritis.

TABLE IV. MORBIDITY IN DIAGNOSTIC CURETTAGE

METHOD OF TREATMENT	NUMBER OF CASES	MORBID		NONMORBID	
		NO ANTIBIOTICS	ANTIBIOTICS	NO ANTIBIOTICS	ANTIBIOTICS
1. Conservative	21	2	1	8	10
2. Operative	12	6	0	2	4

Table V confirms the findings in the two groups discussed above and lists all the perforations with the various methods of management. The patient's morbidity has been consistently decreased when a conservative plan has been followed and, needless to say, the hospital stay has been considerably shortened.

TABLE V. MANAGEMENT AND COURSE OF ALL CASES

METHOD OF TREATMENT	NUMBER OF CASES	MORBID		NONMORBID	
		NO ANTIBIOTICS	ANTIBIOTICS	NO ANTIBIOTICS	ANTIBIOTICS
1. Conservative	24	2	1	9	12
2. Operative	27	11	2	3	11

Two patients not listed in the tables had curettements because of hydatidiform moles. In one of these a hysterectomy was performed because abundant molar tissue was present within the uterine cavity and was found in the myometrium. No tissue was recovered in the other patient so the perforation

was repaired through an abdominal incision. This latter patient was followed for six months and made an uneventful recovery.

There was one death in this series in a patient who developed peritonitis following an unrecognized perforation which occurred following insertion of radium for carcinoma of the cervix. The patient did not have the benefit of antibiotic therapy.

Frequently the operator feels compelled to explore the abdomen following a perforation in the fear that other intra-abdominal trauma has resulted. There were but two instances of this type encountered in this series. A small tear was found in the mesocolon in one patient which was not bleeding and probably required no repair although this was carried out. The uterus in this case was perforated with an ovum forceps and undoubtedly represents a delay on the part of the operator in recognizing the accident. In an effort to confirm the presence of a perforation in another patient the curette was reintroduced and upon withdrawal the right Fallopian tube was brought through the uterine wound. A right salpingectomy was performed through an abdominal incision. The operator in this instance would have done well to use a blunt sound to confirm his suspicions rather than a curette. The first of the cases with additional injury would probably have done well even if the rent in the mesocolon had been unrecognized. The complicating factor in the second patient was obvious and its management presented no problem.

On the basis of the findings in 51 patients with accidental perforations of the uterus a conservative plan of management seems to be indicated. The uterus is always palpated and the cavity sounded for position and depth prior to introduction of a curette. If the uterus is larger than 10 weeks' size in a patient with an incomplete abortion, she should receive 1 c.c. of Pituitrin and the larger portions of tissue should be removed with an ovum forceps or sponge stick to allow the uterus to contract somewhat before the curette is employed. It is not uncommon to perforate the uterus with the first gentle introduction of the uterine sound. When accidental perforation of the uterus is recognized or suspected further curetting should be immediately discontinued. The presence of a perforation may be confirmed by the careful introduction of a blunt sound. Obviously sharper instruments should never be used for this purpose. In the absence of evidence of infection in the uterine cavity the patient can now be carefully observed for evidence of peritonitis and intraperitoneal hemorrhage. Should the uterine cavity contain infected material, laparotomy and closure of the perforation should be carried out. With present-day aids to the treatment of infection it is difficult to conceive of an instance in which hysterectomy would be required. This remark does not apply, of course, to the patients whose injury resulted from criminal abortion under unknown circumstances. The remaining patients, if there is no immediate obvious evidence of other injury, should be placed on intensive antibiotic therapy. Frequent checks of pulse, temperature, and blood pressure and careful examinations of the abdomen should follow during the next 48 hours; signs of hemorrhage or infection should then be the basis for laparotomy. During this period of observation oral feedings should be omitted and the patient maintained on intravenous fluids in the

event that bowel injury has occurred. Enemas should also be omitted for the same reason. Although perforation was followed by the abandonment of further efforts at curettement, all patients with incomplete abortion have spontaneously evacuated the uterus. In the absence of external uterine bleeding it is probably wise to avoid the use of oxytocics during the first 48 hours as an increased uterine tone might conceivably add to the possibility of spillage of uterine contents through the defect into the peritoneal cavity. The decision to open the abdomen will sometimes be based on minimal evidence of intra-abdominal infection or injury. The attendant would be careless to wait for overwhelming signs and symptoms of such complications to develop. Therefore it is anticipated that under this regime occasional unnecessary explorations may be carried out.

Summary and Conclusions

1. Fifty-one patients with accidental perforation of the uterus which occurred during diagnostic or therapeutic curettement are presented and their course and management discussed.

2. One death resulted in an unrecognized perforation following the insertion of radium. Other serious injury or complication has not resulted. All accidents happened under favorable conditions in a hospital operating room.

3. Patient morbidity was lowest in those patients treated conservatively.

4. The role of antibiotic therapy is stressed.

5. A plan for conservative management is outlined.

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CERVICAL CARCINOMA IN SITU: DIFFICULTIES IN DIFFERENTIAL DIAGNOSIS*

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ONE of the most baffling problems facing the gynecologist today is the entity best known as "carcinoma in situ" of the cervix. This describes squamous-cell carcinoma during that phase of its development when it is still within the confines of the surface epithelium, its site of origin.

In theory, all agree that cervical carcinoma passes through an intraepithelial phase before it begins to invade the stroma. The morphologic characteristics of carcinoma in situ, as variously described, include marked anaplasia, hyperchromatism, polynucleosis, disparity in the size, shape, and staining quality of the nuclei, disturbance in the nuclear-protoplasmic ratio, increased mitotic activity, abnormal mitotic figures, loss of polarity, loss of layering and disorderly arrangement, and an intact basement membrane.

Application of Term "Carcinoma in Situ"

With apparently so clear-cut a picture, it might be expected that this entity would offer little difficulty. In practice, however, there is considerable confusion as to the proper application of the term "carcinoma in situ" and consequent uncertainty as to the management of lesions so designated. This is largely attributable to the fact that changes of the epithelia fulfilling all the cytologic criteria of this lesion have been seen to regress or at least not to eventuate in invasive carcinoma, though untreated.[1, 2]

Despite the obvious implication that such lesions do not always represent an early phase of carcinoma, some observers[3] apply the term carcinoma in situ to all cases which present this histologic picture, without concern as to the outcome. The authors define this term strictly as a lesion which will inevitably lead to invasion and death in the absence of treatment. "Carcinoma" has a very special meaning, which includes *irreversibility* as an irreducible minimum, and, though qualified by "in situ," may not properly be applied to any case for which the possibility of regression is admitted. The matter of terminology is of more than academic interest, for it tends to influence the mental attitude of physician and patient alike. If "carcinoma in situ" is the diagnosis, the lesion, by implication, is declared "guilty" until proved innocent, and there is a strong temptation to employ radical treatment, which would be unnecessary in those cases that would regress.

A more acceptable term for histologically cancerlike lesions, whose outcome is unpredictable, would be one that alerts but does not alarm, and

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ensures persistent, thorough investigation to determine whether the atypical epithelium is benign or irrevocably embarked on a lawless career. Such a term as "suspiciously atypical," for example, assumes the lesion to be innocent until proved otherwise and puts it on probation under close supervision, so that effective measures for its arrest may be instituted at the first sign of malignant propensities.

Even more important than terminology is the question of the true significance of these atypical lesions. Granting that they are not invariably followed by an invasive neoplasm, in what percentage may we expect this to happen? Where malignancy develops, is it an outgrowth of the atypical epithelium or is the relationship purely coincidental?

Solution of these problems has been hampered by difficulties that have thus far proved insurmountable. Most serious handicap is the fact that pathologists are still admittedly limited in their understanding of the cytologic characteristics of the incipient squamous-cell carcinoma.[4] Schottlaender and Kermauner's[5] suggestion that the picture of intraepithelial carcinoma is duplicated in the noninfiltrating atypical epithelium sometimes found at the margin of the frank, invasive growth has been accepted by many without challenge. Actually, however, there is no proof that this is so. In fact, an altogether different interpretation is suggested by the finding[6] of similar atypical changes at a short distance from the margin. Moreover, similar changes may be associated with nonmalignant conditions, such as pregnancy, erosion healing, and other nutritional, degenerative, and inflammatory reparative processes. This would suggest that the atypical epithelial changes seen at the edge of invasive neoplasms are not an early stage in the development of malignancy, but a reaction of the normal epithelium to influences emanating from the adjoining neoplasm. This possibility was earlier considered by Schiller,[7] but was as quickly dismissed by him and has received little or no attention since then. However, in the absence of evidence to the contrary, it merits serious consideration.

Clarification of the "in situ" problem has also been hampered by lack of agreement as to what constitutes invasion, the sole criterion which distinguishes the extraepithelial from the intraepithelial carcinoma. To support a diagnosis of invasive carcinoma, most observers, including ourselves, require extension of the atypical cells beyond the basement membrane with infiltration of the stroma. Until recently, some observers[8] accepted extension into the cervical glands as sufficient. Since these offer free access, entrance into them obviously requires no exercise of invasive power and is therefore not necessarily proof that the cells possess or are exercising such power. Indeed, the presence of squamous cells within the glands is a common finding in healing erosions and other benign proliferations. To accept it as proof of invasion opens the way to false positive diagnoses of invasive carcinoma.

At the other extreme, loose interpretation of invasion has led some observers[2, 3] to classify as carcinoma in situ cases of early invasion, on the assumption that "minimal" invasion does not exclude a lesion from the "in situ" category. The situation is further complicated by the fact that con-

siderable experience is necessary before the pathologist can recognize very early invasion when he sees it or, conversely, recognize as benign lesions that *appear* to invade. In some very doubtful cases, even the most expert pathologist may find himself baffled.

Efforts to improve our understanding of carcinoma in situ have encountered an obstacle in the paucity of material available for study. At best, only a limited number of squamous-cell carcinomas are likely to be detected while still intraepithelial, inasmuch as they are clinically symptomless at this stage. Even where substantial series of supposed "in situ" cases have been collected, resort to radical measures, which remove or destroy the atypical epithelium, has reduced the number of cases available for follow-up study. Retrospective material, in the form of cervical biopsy specimens previously obtained in known cases of invasive carcinoma, has thus far also proved relatively scanty. In our own experience,[9] for example, we could find only 9 such cases among more than 4,000 cervical biopsy specimens examined during a period of 16 years.

Material Studied

With the hope of throwing some light on this problem, we began, in the latter part of 1950, an investigation of all cervical biopsy material that passed through the Gynecologic Division of the Department of Obstetrics and Gynecology of the Jefferson Medical College Hospital since 1930. In a previous communication, we[9] reviewed our findings among 4,152 cervical biopsy specimens obtained between 1930 and 1946 from patients hospitalized for gynecologic disorders. We propose here to summarize these findings briefly and add the findings among 4,187 specimens obtained between June 1, 1946, and May 31, 1952.

Between 1930 and 1946, when the Department of Pathology was under the direction of the late Dr. B. L. Crawford and, more recently, under the late Dr. C. J. Bucher, the major part of the histologic diagnoses for the Gynecologic Division were made by one of us (J. H.), who diagnosed squamous-cell carcinoma on the basis of the characteristic morphologic changes of malignancy plus evidence of invasion, as taught him by Robert Meyer. As proof of invasion, we accept any change which indicates that the squamous cells have begun to exercise their invasive powers beyond the surface epithelium. This must take the form of an actual break through the basement membrane of the surface epithelium or, where the cells have entered the cervical glands, through the membrane which separates them from the surrounding stroma. The break may be minimal, being evident only in a dissolution of the membrane preliminary to actual migration of the malignant cells into stromal territory. If such a break is demonstrable anywhere in the cervix, the case is classified as invasive even though in some slides the lesion appears entirely intraepithelial.

Retrospective Material.—

In our 1930 to 1946 series, invasive squamous-cell carcinoma was found in 474, or 11.4 per cent, of 4,152 cervical biopsy specimens. In only 9 were there available for review one or more biopsy specimens obtained 7 months to 9

years before. These were re-examined with the view of discovering any instances of carcinoma in situ overlooked by reason of our insistence on proof of invasion for a diagnosis of malignancy.

In 3, the original diagnosis of "no malignancy" was confirmed: 2 showed benign polyps, 1 chronic cervicitis. None of the 3 showed changes which might support an "in situ" diagnosis. In 3 others, the original diagnosis was "suspicious of malignancy but tissue insufficient to establish invasion." These were likewise confirmed on review. One of these was particularly noteworthy because of the more than 8 years' interval between the first suspicious biopsy, which showed fading of the basement membrane, suggesting beginning invasion, and the final diagnosis of frank invasive carcinoma. In 2 other cases, the original diagnosis of "suspicious but no evidence of invasion" proved erroneous. One of these was originally diagnosed by another pathologist, who judged the lesion to be benign because he could find no evidence of invasion of the stroma. On review, a definite breakthrough could be observed. The second was originally diagnosed by one of us (J. H.) as "cervical erosion; very suspicious of malignancy; case should be watched." On review, we noted changes very suggestive of early invasion. For confirmation, we recut the original block: the new sections left no doubt as to the diagnosis. These 2 cases emphasize the importance of a careful search for even the slightest evidence of a breakthrough, which may otherwise be missed in the very early carcinoma. In both these cases, beginning invasion preceded the final diagnosis of frank invasion by 4 years.

In only 1 of this group of 9 cases did the previous specimens present changes which would justify a diagnosis of true intraepithelial carcinoma in the strict sense of an irreversible lesion certain to invade if untreated. There were 4 previous biopsies, the first obtained almost 4 years before invasion was finally established. Another pathologist originally described "marked hyperplasia and hyperkeratosis of the squamous epithelium, suggestive of malignancy," but finding the submucosal tissue too scant to determine infiltration, he requested another deeper biopsy. In the second specimen, provided almost 3 years later, one of us (J. H.) originally noted a thick, stratified and cornified layer of squamous epithelium with atypical basal cells and suggested it might be a slow malignant growth. Observing no stroma, we requested another deeper biopsy and recommended that the case be watched. The third and fourth specimens were provided within the next 2 months. The surgeon described the tissue as "coming away in strips." Neither specimen included underlying stroma. Of both, another pathologist said "very suggestive of malignancy; suggest deeper biopsy to determine infiltration." Not until 6 months later did biopsy yield submucosal tissue revealing invasion of the stroma. On review, the original reports were confirmed. In this interesting case, we were apparently dealing with a predominantly exophytic growth which, at least in those portions accessible for purposes of biopsy, remained intraepithelial for some time.

Follow-up of Atypical Lesions.—

To make sure we had missed no in situ carcinomas among our group of benign cervical specimens, these were also reviewed. Among 2,377 benign cervical erosions, we found 37 which showed very marked epidermization of the surface and glands with atypical cellular changes reminiscent of those seen in malignant neoplasia. In addition, among 885 polyps, we found 7 which showed similar atypical changes. All 44 were diagnosed as benign but the clinician was apprised of their bizarre appearance and follow-up was recommended. On review, we could find no reason to revise our original impression of their benign though alarming appearance. In 17, personal follow-up records of 5 to 20 years were available to substantiate our original diagnosis.

In 2, personal follow-up records of 1 and 3 years without malignancy were available. Unfortunately, there was no follow-up for the remaining 18 cervical erosions and 7 polyps. However, the failure of these patients to appear in the records of our Follow-up Pelvic Malignancy Clinic or other hospital departments, and their absence from the list of pelvic cancer deaths is at least presumptive evidence that they remained free from cervical carcinoma. The possibility of their removal from this area cannot, of course, be discounted. Additional assurance of the outcome, at least so far as the 7 polyps are concerned, may be derived from Meyer's[4] statement that such polyps, though often alarming in appearance, are seldom if ever carcinomatous except secondarily by reason of invasion at the base. Our experience confirms this. Of the 887 polyps in our series, only 2, or 0.225 per cent, showed malignant changes, which were clearly an extension from the cervical mucosa.

Our incidence of true carcinoma in situ between 1930 and 1946 was thus only 1 in 4,152 cases, or 0.02 per cent. This is well within the theoretical limit set by Taylor,[10] who estimated, on the basis of the known incidence of invasive cervical carcinoma in the population, that 0.3 per cent is the maximum possible detection rate of intraepithelial carcinoma in gynecologically symptomless patients. Actually, the reported figures range from 0.3[11] to 3.9 per cent.[12] To explain these figures, Taylor suggests that the "group is not truly unselected, that the laboratory is not applying correct histological criteria, or that a considerable proportion of so-called intraepithelial lesions are either reversible or progress so slowly that they will not result in clinical carcinoma within the life span of the patients." That these larger series may include benign reversible lesions has also been suggested by McKelvey,[13] who speaks of "an atypical form of exaggerated erosion healing."

Were we to include our 44 atypical but benign lesions among our in situ carcinomas, we would arrive at a figure of 1.02 per cent. If, in addition, we added cases showing minimal invasion, which some count among their "in situ" cases, we could approximate the larger reported figures even more closely. However, in view of the results of our follow-up studies, it would seem more accurate to retain our 44 histologically cancerlike lesions in the category of benign lesions that require watching. To classify them as "in situ" or Group 0 carcinoma and imply that their failure to develop into invasive carcinoma represents spontaneous regression or, in the treated case, a "cure," would be misleading and would give rise to the impression that noninvasive carcinoma is reversible or will respond readily to local measures. This could prove a most dangerous assumption in the case where minimal invasion is either missed or dismissed as within the limits of the definition of noninvasive carcinoma. Local measures in such cases are likely to prove inadequate and open the way for a recurrence. The literature[15, 16, 17] indicates that even more far-reaching measures, such as total hysterectomy or supposedly cancerocidal radiation, may be inadequate in the "superficial carcinoma." Such experiences suggest that the truly malignant lesion need not progress far into the depths of the cervix to enable the malignant cells to reach a locale where they are safe, not alone from biopsy and cauterization but even from hysterectomy and irradiation. It would follow that, even where there is only minimal invasion, it must be attacked as vigorously as the more deeply infiltrating lesion.

To understand why genuine intraepithelial carcinoma is bound to be rare, even in the most selected series, it is necessary to recall that the malignant transformation begins in the basal layer of the surface epithelium,[4] whence the malignant cells may progress upward through the normal epithelium and/or downward into the stroma. How rapidly they will progress in any direction will depend, of course, upon the inherent invasive power of the growth

and the resistance of the host. Whether their downward or upward progress will be more rapid will depend on the relative resistance of the surface epithelium and stroma. If equally permeable, progress in both directions may be equal. Their stromal progress will be facilitated in the presence of inflammation or granulation tissue, or retarded if the stroma is unduly resistant.[4] Only in the latter situation is the carcinoma likely to remain intraepithelial long enough to be detected before invasion. Our experience and that of others[4, 18] would indicate that such cases are exceptional.

Cervical Biopsy Material Between 1946 and 1952.—

More accurate statistics regarding the incidence and curability of carcinoma in situ, and a better understanding of the earliest stages of cervical carcinoma will be possible only through critical analysis of a large amount of material, made available by routine cervical biopsy performed without reference to gynecologic symptomatology. Since 1946, it has been the policy of our Gynecologic Division to do as much as possible to improve our chances of detecting early carcinomas. Toward this end, we have closely followed all patients in whom a biopsy diagnosis of epidermization has been made. Between Jan. 1, 1949, and Dec. 31, 1951, a total of 93 such patients were encountered; all have thus far shown no evidence of cervical carcinoma. We have also done chiefly circular cervical biopsy in all patients who have come to operation, except those hospitalized for dilatation and evacuation because of incomplete abortion. In addition, since July, 1951, 75 patients in the outpatient department were biopsied routinely without reference to the appearance of the cervix. Of these, 2 showed invasive carcinoma: one showed clinical evidence of malignancy; the second appeared clinically suspicious.

TABLE I. TYPES OF LESION AMONG CERVICAL BIOPSY SPECIMENS (1930-1952)

	1930-1946		1946-1952	
	NO. CASES	%	NO. CASES	%
Benign.—				
Normal mucosa	143	3.4	196	4.68
Cervical erosion	2,377	57.2	—	—
Chronic cervicitis	—	—	3,204	76.5
Cervical polyp	885	21.3	461	11.01
Miscellaneous (myoma, etc.)	233	5.6	94	2.2
Malignant.—				
Squamous-cell carcinoma	473	11.38	211	5.03
Carcinoma in situ	1	0.02	9	0.21
Adenocarcinoma	39	0.9	10	0.23
Adenoacanthoma	—	—	1	0.02
Sarcoma	1	0.02	1	0.02
Total no. specimens	4,152	100.00	4,187	100.00

Between June 1, 1946, and May 31, 1952, 4,187 cervical biopsy specimens were studied. The histologic diagnoses were made by Dr. P. A. Herbut (head of the Department of Pathology) and Dr. R. L. Breckinridge (in charge of the hospital laboratory), who have cooperatively made the material available to one of us (J. H.). In addition, outside pathologists have also been consulted. The types of lesion encountered are presented in Table I, along with those in our 1930 to 1946 series, for purposes of comparison.

Invasive squamous-cell carcinoma was reported in 211 cases, or 5.03 per cent. In 9 cases, or 0.21 per cent, the diagnosis made by the Department of Pathology was "carcinoma in situ," "probable carcinoma in situ," "marked epidermization which some call carcinoma in situ," and, in one pregnant

patient, "carcinoma in situ conditional upon confirmation post partum." In several of the cases, concurring opinions were obtained from outside pathologists of national repute. Of the 9 cases, 5 were private and 4 ward patients.

Follow-up in 6 Cases Diagnosed "Carcinoma in Situ."—

For the 4 ward patients, a policy of watchful waiting was adopted. Table II summarizes the findings in this group plus 2 additional cases, one encountered before June, 1946, the other after June, 1952. One of us (J. H.) diagnosed all 6 cases as "benign though alarming atypism"; in Case 2, preliminary inspection at first suggested early invasion, but more careful study prompted a revision to "benign though alarming atypism."

TABLE II. FOLLOW-UP IN 6 UNTREATED CASES DIAGNOSED "CARCINOMA IN SITU"

Case No.	1 (C. H.)	2 (E. W.)	3 (D. J.)	4 (W. R.)	5 (D. H.)	6 (M. N.)
Age (years)	20	27	40	30	30	32
Race	White	Negro	Negro	Negro	Negro	Negro
Hormonal status	Pregnant	Nonpregnant	Nonpregnant	Nonpregnant	Nonpregnant	Pregnant
Papanicolaou test	Doubtful	Negative	Negative	Suspicious	Suspicious	Suspicious
Evidence of infection						
Chronic P.I.D.	—	—	Present	Possible	—	—
Inflammatory reaction	Marked	Marked	Marked	Intense	Marked	Marked
Trichomonas	Present	Present	Present	—	Present	—
Suspicious cervical biopsy	2/12/46	5/10/51	7/ 7 /51	1/12/52	3/31/52	11/ 1 /52
Repeat cervical biopsy	10/15/46	10/ 8 /51	12/11/52	3/10/52	12/ 6 /52	12/15/52
Interval since first biopsy	8 months	5 months	1 year, 5 months	2 months	8 months	6½ weeks
Histologic diagnosis	Benign	Benign	Benign	Benign	Benign	Less atypism

The average age of these patients was 29.8 years. All but one were Negroes. In 3, the possibility of malignancy was first suggested by cytologic examination of vaginal and cervical smears; in the remaining 3, smears taken shortly before or coincident with the suspicious biopsy specimen, were "doubtful" in one and "negative" in two. In all 6, the vaginal smear reports noted an associated marked or intense inflammatory reaction, while in 4 trichomonads were present. Pelvic examination revealed evidence of pelvic inflammatory disease in one and was suggestive of such disease in another.

Two (Cases 1 and 6) were pregnant. Case 1, first seen 6 years ago, was previously reported by us[9] among our 37 cases of benign though alarming cervical erosion. It is now included with this group because our Department of Pathology and a prominent consultant pathologist diagnosed it, "carcinoma in situ" and "invasive carcinoma," respectively (Fig. 1). On the basis of the latter diagnoses, this 20-year-old white woman would have been treated radically except that her husband was not available to give his consent. Cervical biopsy, performed 3 months after delivery by cesarean section and 8 months after the original suspicious biopsy, showed a benign cervical mucosa (Fig. 2). This patient has remained free from cervical malignancy to date.

The second pregnant patient, a Negro woman, aged 32 years, was near term when the "in situ" diagnosis was made. A second biopsy was performed 6 weeks after delivery and less than 7 weeks after the suspicious biopsy specimen was obtained. Our Department of Pathology reported the finding of a hyperplastic cervical epithelium with many atypical cells similar to the

original biopsy, but the atypism was stated to be less extensive than before. The submucosa was described as heavily infiltrated with inflammatory cells. In view of the short interval between the second biopsy and the termination of pregnancy, it is not surprising that only partial regression had occurred. Though still "on probation," the lesion would seem to be moving away from rather than toward malignancy.

In the 4 nonpregnant patients, repeat biopsy followed the diagnosis of "carcinoma in situ" within 2, 5, 8, and 17 months, respectively. In every instance, the original alarming atypism had regressed and a diagnosis of

Fig. 1.

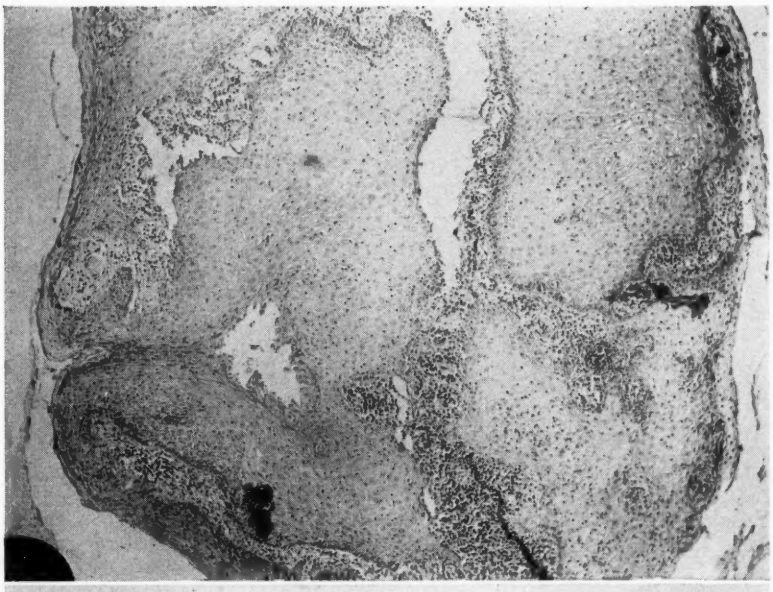

Fig. 2.

Fig. 1 (Case 1, C. H.).—Cervical biopsy specimen obtained from a 20-year-old white woman in the third month of gestation, diagnosed "carcinoma in situ" by the Department of Pathology and "invasive carcinoma" by a prominent consultant pathologist.

Fig. 2 (Case 1, C. H.).—Cervical biopsy specimen showing benign mucosa, obtained 3 months after delivery by cesarean section and 8 months after the first suspicious biopsy. To date, 6 year follow-up without cervical carcinoma.

chronic cervicitis was made (Figs. 3 to 8). To date, their benign status remains unchanged.

This group emphasizes the difficulties in the differential diagnosis between benign atypia and early cervical carcinoma. Even in expert hands, these carcinomimetic lesions may be confused not only with intraepithelial but at times even with invasive carcinoma, particularly where the atypical

Fig. 3.

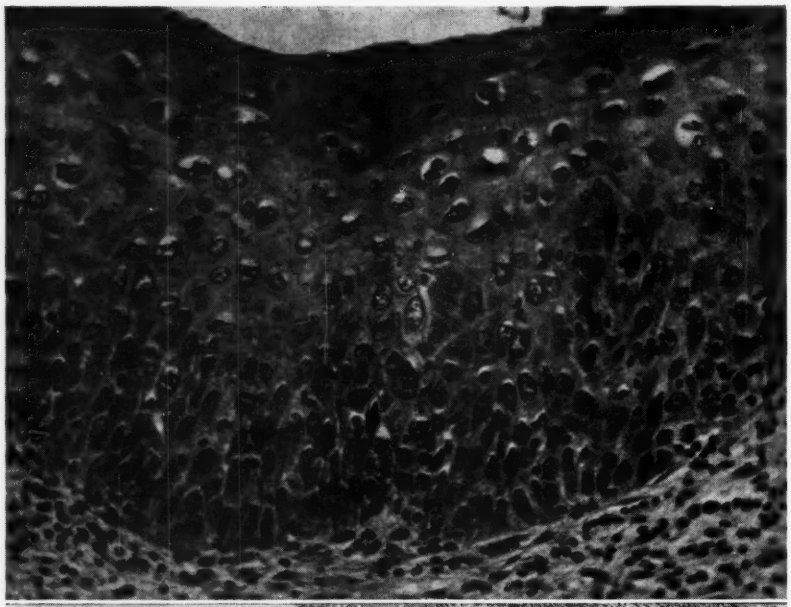

Fig. 4.

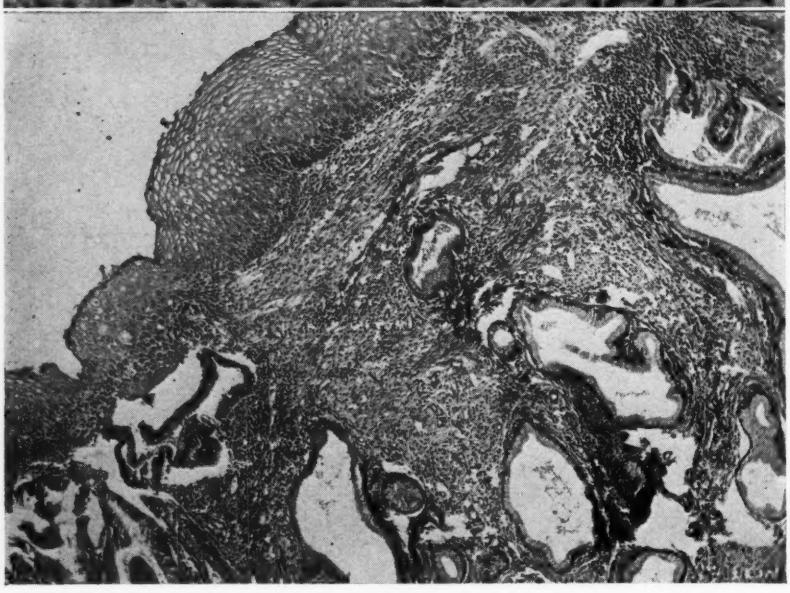

Fig. 3 (Case 2, E. W.).—Cervical biopsy specimen obtained from a 27-year-old nonpregnant Negro woman, diagnosed "carcinoma in situ."

Fig. 4 (Case 2, E. W.).—Cervical biopsy specimen showing benign mucosa, obtained 5 months after first suspicious biopsy.

cells fill the deep-lying glandular lumina. Our experience with this group also demonstrates the value of watchful waiting where the true nature of the lesion is in doubt.

Etiology of Carcinomimetic Lesions

The associated findings in these 6 cases point up the part played by inflammatory disease in the etiology. It is noteworthy that an associated

Fig. 5.

Fig. 6.

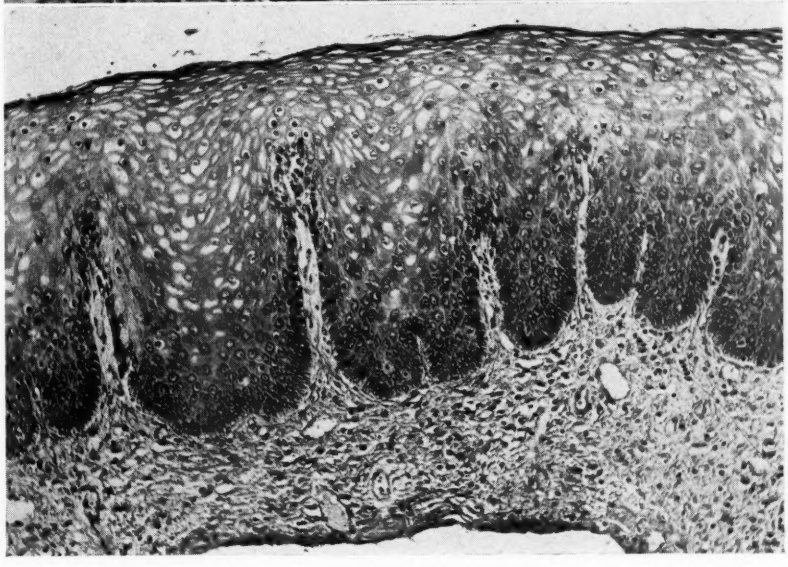

Fig. 5 (Case 4, W. R.).—Cervical biopsy specimen, obtained from a 30-year-old nonpregant Negro woman, diagnosed "carcinoma in situ."

Fig. 6 (Case 4, W. R.).—Cervical biopsy specimen showing benign mucosa, obtained 2 months after first suspicious biopsy.

inflammatory reaction was also observed in 10 of our 37 "carcinoid" lesions previously reported.[9] McKelvey[13] noted among his atypical cases patterns with "a very frequent and relatively massive underlying inflammatory-cell infiltration." Scheffey, Rakoff, and Hoffman,[19] who studied vaginal smears and cervical biopsy specimens, obtained concurrently from 500 consecutive patients of the gynecologic ward, found that "pelvic inflammatory disease is more likely to be responsible for a false positive smear than any other type of lesion." Similarly, Dellepiane,[20] who employs a modified cytologic method that stresses nuclear changes, found that cervical erosions of inflammatory origin were a not infrequent cause of false positive and doubtful diagnoses of cervical malignancy.

That pregnancy also plays a part in the etiology is suggested by the two cases in which atypia appeared during gestation and regressed in whole or in part after its termination. There is abundant evidence[2, 21, 22] that atypical changes are more common in the pregnant than in the nonpregnant cervix. It would appear that the hyperhormonal, vascular, and other conditions incident to this state favor hyperactivity of the cervical epithelium and atypical cellular modifications.

Atypical cancerlike epithelia also occur in the postmenopausal cervix.[7] Among 100 in situ carcinomas collected by Kottmeier,[1] 58 were at or past the climacteric. In a preliminary sampling of vaginal smear reports on patients at or past the menopause, we observed a fairly frequent association of atypical cells suggestive of malignancy, marked estrogen deficiency, and an intense inflammatory reaction. Conceivably, atypical changes in the postmenopausal cervix may be due to lack of the protective influence of estrogen, which makes such women more vulnerable to infection with a correspondingly more intense inflammatory reaction. This, together with the modifications incident to regression of the cervical epithelium, may account for the alarming atypism encountered in some cases.

Recent reports[23, 24] have stressed the role of Trichomonas infestation in the etiology. This was present in 4 of our 6 cases, but its importance should not be overestimated in view of the fact that in many cases with trichomonads, the cervical epithelium is within normal limits. Thus, among 825 vaginal smears taken consecutively from patients of the Obstetric Division of our Department during the first 11 months of 1952, 215, or 26.06 per cent, showed trichomonads, but only 1, Case 6 previously mentioned, showed cervical cells suspicious of malignancy, as reported to us by Dr. A. E. Rakoff, Director of the Cytology Laboratory.

Since epithelial atypism simulating neoplasia is not a frequent finding in pregnancy, the natural and artificial menopause, inflammatory cervical erosions, trichomoniasis or other infections, it seems likely that not one but several factors combine in a given case to produce a degree of atypism suggestive of malignancy. Local tissue reactivity probably also plays a part, so that hormonal, infectious, and other influences, which produce alarming atypism in one individual, may fail to do so in another with a less responsive mucosa. The high proportion of Negro women among our 6 "carcinoma in situ" cases is of interest in this connection. This is in line with the fact that

some of the highest percentages of cases with this lesion have been reported from southern clinics.[12] Whether this predominance is attributable to unusual tissue reactivity or to a higher incidence of pelvic infection, we cannot say.

Differential Diagnosis

The problem presented by the markedly atypical cervical epithelium is thus far from simple. Since the cytologic characteristics ascribed to carci-

Fig. 7.

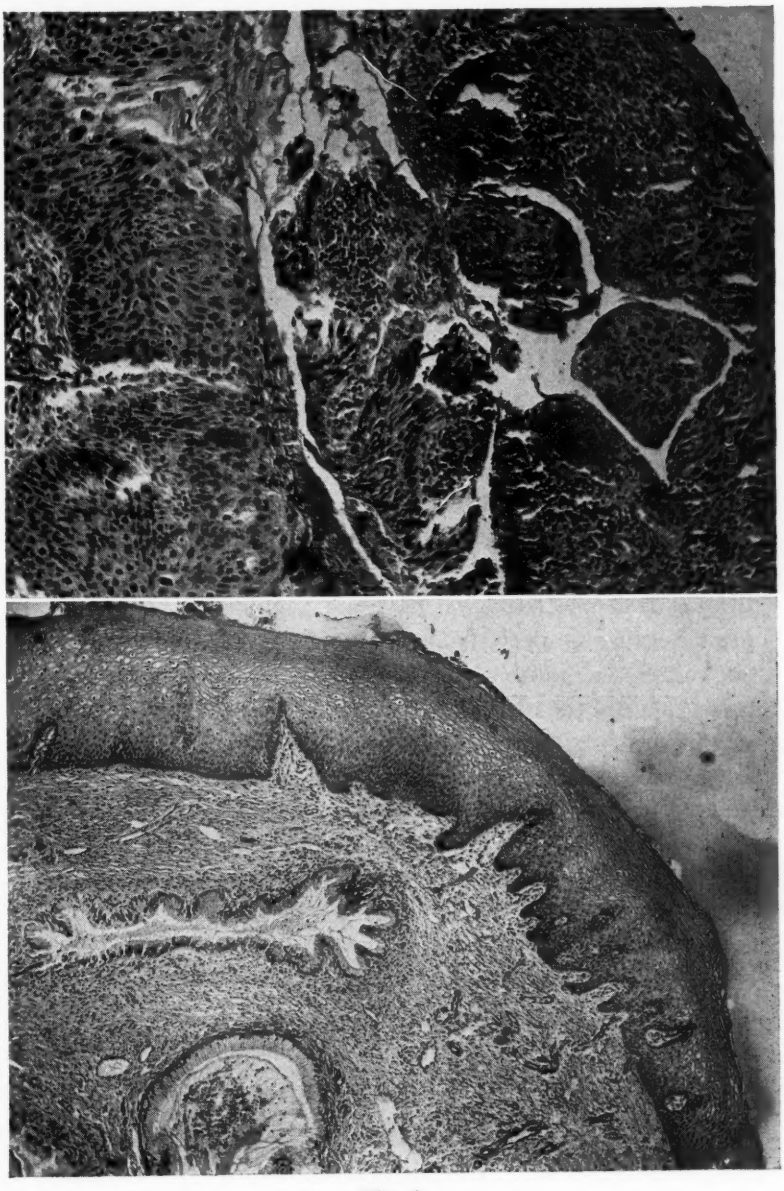

Fig. 8.

Fig. 7 (Case 5, D. H.).—Cervical biopsy specimen obtained from a 30-year-old nonpregnant Negro woman, diagnosed "carcinoma in situ."

Fig. 8 (Case 5, D. H.).—Cervical biopsy specimen showing benign mucosa, obtained 8 months after first suspicious biopsy.

noma in situ may be found either singly or in combination in benign reversible atypia, no single characteristic or group of characteristics may be considered specific to either. Indeed, as pointed out by Bechtold and Reicher,[23] benign atypia may sometimes present a more alarming degree of atypism than genuine carcinoma. On the basis of a careful study of the cellular picture in the 6 cases reviewed above as well as other similar cases illustrated in the medical literature, we should like to call attention to a feature that may perhaps aid in the differential diagnosis between carcinomimetic lesions and genuine incipient carcinoma.

We have been impressed by the relatively *large* size of the atypical epithelial cells and by the presence of giant cells and other mitotic anomalies, which create an impression of considerable *variability* in the size, shape, and staining quality of the cells which compose these lesions. Though a common finding in the late, invasive neoplasm, these changes are not typical of the very early carcinoma. In our experience and that of others,[4] the very young neoplasm does not show the flagrant deviations from normal seen in the older cancer. Stemming as it does from the basal cells of the surface epithelium, the beginning carcinoma is composed of *small,* closely packed unripe or middle-ripe cells, whose nuclei are somewhat irregular and somewhat darker than those of the normal epithelium. Mitoses and mitotic anomalies are usually absent except—significantly—in the presence of severe inflammation.[4] As a result, the young uncomplicated neoplasm gives the impression of relative *uniformity* in the size, shape, and staining quality of the nuclei as well as in the density of the cell population. This would suggest that the extreme degree of atypism found in the older tumor is at least partly attributable to inflammatory and other degenerative changes superimposed upon it as it enlarges and ages. Granting this, it follows that such extreme atypism is not pathognomonic of uncomplicated beginning carcinoma and, where found in the absence of invasion, does not per se justify a diagnosis of true intraepithelial carcinoma. On the contrary, it seems likely that such changes, whether found at or near the margin of an invasive neoplasm or in its absence, do not represent an early phase of malignant transformation but are simply a nonspecific reaction of normal cells to injurious influences in the environs.

In this connection, Wespi,[24] who may be counted among those friendly to the "in situ" hypothesis, recently pointed out that existing statistical data relating to the age distribution of "carcinoma in situ" do not support the assumption that this lesion is an invariable precursor of invasive carcinoma. Rather the evidence indicates that it is a distinct entity in some way related to the sexual hormones and, at best, may be said to be a forerunner of invasive carcinoma in only a small percentage of the cases. For the rest, the initial phase apparently takes some other form as yet to be determined.

Need for Conservatism

A final answer must wait upon further investigation of incipient cervical carcinoma. In the meantime, the pathologist must expect to face a period of anxious indecision in the doubtful case. His first step should be a careful examination of multiple sections to determine whether there is invasion near

by. Where the specimen includes the margin of the lesion, it may be possible to determine whether the atypical cells possess invasive powers by searching the contact area for evidence that they are insinuating themselves between their normal epithelial neighbors and destroying the latter as they encompass them. This process of "self-invasion"[23] or "functional conflict"[13] between the malignant and normal epithelium was earlier noted by Meyer[4] and more recently by McKelvey[13] and others.[23] Unfortunately, clear-cut evidence of such intraepithelial invasive activity is not always demonstrable.

Failing proof of invasion, a policy of watchful waiting is indicated. The responsibility of the pathologist and clinician is a heavy one. There is a strong temptation to take the easy way out, namely, radical therapy, which is a certain guarantee against recriminations for undertreatment. Blame for overtreatment, on the other hand, must rest entirely on the word of another pathologist, who can never hope to produce conclusive evidence of his contention that the lesion was benign and would have regressed. Radical therapy may be justified in the older woman, who has little to lose if her reproductive function is destroyed. Unfortunately, suspiciously atypical epithelia are often encountered in younger women to whom loss of reproductive potential and premature onset of the menopause are serious considerations.

Granting that conservatism is indicated in such cases, how long may one expect to wait? If we may judge from Meyer's[4] experience, the atypical epithelium destined to become malignant is likely to show minimal evidence of invasiveness, sufficient to resolve all doubt, within a few weeks or months. On the other hand, recent reports[23, 25] indicate that carcinomimetic atypia, traceable to infection, regress after a few weeks under appropriate medical measures aimed at the infection. Our experience and that of others[2, 22] indicate that atypia associated with pregnancy will regress sufficiently to establish their benign, reversible character within a few months after delivery. Thus, the period of waiting need not be long. In the case headed for malignancy, the brief delay may not seriously lessen the curability of the lesion at this early stage. On the contrary, certain proof of its malignant character will encourage an "all-out" attack, without which even the early lesion may sometimes recur.

Summary

1. Existing confusion regarding carcinoma in situ of the cervix and reasons for delay in clarification of the problem are discussed.

2. Our findings among 4,152 cervical biopsy specimens, obtained between 1930 and 1946 and previously reported, are briefly summarized, with particular emphasis on 9 invasive carcinomas with previous biopsy specimens, among which 1 true intraepithelial carcinoma was found.

3. The findings among 4,187 cervical biopsy specimens obtained between 1946 and 1952 are presented, with particular emphasis on 6 cases diagnosed "carcinoma in situ" and followed by repeat cervical biopsies without treatment other than the repeat biopsies, which, to date, showed the lesions to be reversible.

4. The etiology of benign carcinomimetic cervical lesions is discussed and the difficulties of differential diagnosis between them and genuine incipient carcinoma are emphasized.

5. Attention is directed to the extreme atypism of such lesions and the suggestion is made that it is not pathognomonic of incipient carcinoma but represents a nonspecific reaction of normal cells to injurious influences in the environs.

6. The desirability of a policy of watchful waiting in the doubtful case, particularly if the patient is young, and the comparative safety of such a policy are stressed.

Conclusions

The "in situ" problem is likely to continue to plague the harried gynecologist for some time to come. Much has yet to be done before the mystery of carcinomatous transformation is penetrated. Until this is accomplished, it is of the utmost importance that we recognize the limitations of our knowledge and adopt a cautious and critical attitude toward any evidence that may be presented.

Our findings among more than 8,000 cervical biopsy specimens would certainly seem to support the conservative point of view, which maintains that true intraepithelial carcinoma is an exceptional finding under the most favorable circumstances with the limited diagnostic facilities at our disposal today.

It is earnestly to be hoped that future research will eventually enable us to recognize beginning cervical carcinoma with certainty and distinguish it with ease from the benign carcinomimetic lesions which are responsible for the confused state of our thinking today.

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Discussion

DR. CLAYTON T. BEECHAM.—There are a number of statements made by Dr. Hoffman with which I do not agree. First, I believe that his theories are based on cases that are not truly carcinoma in situ. If what has appeared on the screen is representative tissue (photomicrocolor), then the paper is based on possibly minor degrees of atypism. Thus, I do not feel that Dr. Hoffman is justified in making statements about the behavior of carcinoma in situ, at least from the material he has studied.

Aside from this, I think we should be extremely cautious about regarding carcinoma in situ as a reversible tissue reaction. This statement has been prompted by some excellent work done by the investigators at Johns Hopkins. However, with regard to these women, whose cervices did return to "normal" following delivery, the final answer is not yet in. No one knows what will ultimately happen.

We clinicians interested in this problem are fortunate to have witnessed the work of the Philadelphia Pathological Society's Committee under Dr. Aegerter, in investigation of this problem. As some of you know, thirteen pathologists from the larger hospitals worked perseveringly to come to an agreement on the diagnostic criteria for what is called "carcinoma in situ" and "atypism." We are fortunate that the pathologists have done this clarifying work, and we as clinicians should follow their criteria.

DR. FARELL (Closing).—Our purpose in presenting this study is to draw attention to our belief that the diagnosis of carcinoma in situ today is being made too often. Many cases so diagnosed are really marked atypism or basal-cell hyperplasia. In other cases further investigation of the tissue may show a truly invasive carcinoma. A true carcinoma in situ does occur, but only rarely. The incidence of carcinoma in situ in 4,187 cervical biopsy specimens as diagnosed by the Department of Pathology of the Jefferson Medical College Hospital was 0.2 per cent, a figure much smaller than is commonly reported.

The six patients reported tonight were all treated conservatively. Repeat biopsies on each of these patients showed no evidence of malignancy. These women are all being followed carefully in the Cancer Follow-up Clinic and are seen at frequent intervals. Answering Dr. Beecham, who questions the diagnoses after only a cursory examination of photomicrographs on the screen, each one of these cases was diagnosed "carcinoma in situ" by members of our Department of Pathology, who participated in the study under Dr. Aegerter and are fully cognizant of the diagnostic criteria to which Dr. Beecham refers. Moreover, in 3 of the 6 cases outstanding pathologists in other cities concurred in the diagnosis.

We are putting these cases on record and it will be interesting to follow them over a period of years to see how they fare.

ESTROGEN METABOLISM IN HUMAN PREGNANCY*†

A Study With the Aid of Deuterium

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and A. E. Rakoff, M.D.,*** Philadelphia, Pa.

(From the Jefferson Medical College)

IT HAS long been believed[1, 2] that estrogen and progesterone are required for the maintenance of normal pregnancy, although their exact individual functions and their modes of action in this respect are still not clearly understood. Furthermore, the progressive rise in the titer of estrogen and progesterone metabolites in the urine[3] as pregnancy advances has suggested that these steroid hormones are required in ever-increasing amounts for the proper fulfillment of their functions in pregnancy.

These steroid hormones are at present extensively employed for treatment or prophylaxis in various pregnancy complications, including threatened abortion, habitual abortion, prematurity, toxemias of pregnancy and diabetes complicating pregnancy.[4] Hormonal therapy for these conditions was suggested largely on the basis that a deficiency of estrogen and pregnanediol have been noted[5-7] in the urine in some patients with these conditions. In some cases there was noted also an elevated titer of chorionic gonadotrophin, particularly in patients with toxemias of pregnancy or diabetes complicating pregnancy. This has been interpreted by the Smiths[5] as indicating inadequate utilization of chorionic gonadotrophin by the syncytium to stimulate adequate secretion of estrogen and progesterone. However, in other instances, particularly in some cases of threatened or habitual abortion, chorionic gonadotrophin as well as estrogen and pregnanediol has been diminished.

Among those who advocate the administration of steroid hormones for these pregnancy complications, there have been two chief schools of thought.‡ One group[9, 10] has suggested that both estrogen and progesterone should be given as such, for direct substitutional therapy. The other school led by the Smiths[11] has suggested that the administration of estrogen alone, particularly diethylstilbestrol, will accomplish the same purpose by favoring the endogenous production of progesterone. It is postulated by the Smiths[11] that diethylstilbestrol shares the property exhibited by certain estrogen oxidation products of stimulating pituitary release of luteinizing hormone and prolactin, which act in synergism with chorionic gonadotrophin to stimulate the syncytium to

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***In the Department of Obstetrics and Gynecology.

‡Another point of view has been presented by H. S. Guterman,[8] who reports that progesterone does not appear to influence the course of threatened abortion.

secrete progesterone and estrogen in progressively increasing amounts. According to these authors,[5] such oxidation products* are formed in maximal amounts when the endogenous production of progesterone is deficient; simultaneously, the metabolic conversion of estrone (and estradiol) to estriol is minimal. On the other hand, in the presence of adequate progesterone, the formation of estriol is favored and that of the estrogen oxidation products is minimal.

Experimental evidence for this "sparing" or retarding action of progesterone on the metabolic breakdown of the estrogens was first obtained by Smith and Smith in 1931, working with rabbits,[12] and in 1932, in women.[13] This was later confirmed and elaborated upon by Pincus and Zahl[14] in 1937 and by Pincus and Graubard[15] in 1940. However, Heard and co-workers[16] could not substantiate this hypothesis; they obtained almost equal recovery of estrogen in the non-pregnant rabbit whether progesterone was simultaneously injected with the estrogen or not. With reference to the latter finding, O. W. Smith[17] pointed out recently that the doses of both estradiol and progesterone administered were very large (300 mg. each) and that it is necessary in women to inject at least 5 times as much progesterone as estrogen in order to influence estrogen excretion to any marked extent.

In view of the importance of the biochemical and clinical implications of the theories which we have so briefly outlined, it seemed very desirable to obtain additional experimental data particularly with respect to estrogen metabolism during pregnancy. The design of our experiments† is outlined as follows. Estrone labeled with deuterium was prepared and injected intramuscularly as the acetyl derivative into two women who were in the last trimester of pregnancy (Experiments 1 and 2). The urine, which was subsequently collected, was hydrolyzed, extracted with ether, and the phenolic material in the ether extracts partitioned into the "estrone," "estradiol," and "estriol" fractions. The amounts of these estrogens were determined by bio-assay, and the deuterium content determined with the aid of a mass spectrometer; this permitted us to make certain calculations, the results of which are indicated in Tables I and II.

TABLE I. URINARY RECOVERY OF ESTROGEN AFTER ESTRONE ACETATE INJECTION

PERCENTAGE OF INJECTED STEROID RECOVERED IN URINE AS:	STEROID INJECTED	
	ISOTOPIC ESTRONE ACETATE (PREGNANT WOMEN*)	NORMAL ESTRONE ACETATE (MEN†)
Estriol	4.0 ; 3.5	3.7 ; 2.7
Estrone + Estradiol + Estriol	Approx. 5.9 ; 7.2	6.0

*This study.
†Pearlman and Pincus.[19]

In Table I, the percentage of the injected hormone recovered in the form of urinary estriol and also as combined urinary estrogens in pregnant women is compared with that obtained in men; the latter experiments were carried out

*These estrogenically inactive products have not been identified.

†The biochemical data have been presented in abstract form[18] and a detailed account will appear in an appropriate journal of biochemistry.

by Pearlman and Pincus[19] in 1943 using nonisotopic estrone acetate. It can be clearly seen that the pattern of estrogen metabolism in both types of experiments is almost identical despite the fact that the endogenous production of progesterone in pregnant women is prodigious by comparison with that in men. According to the theories of the Smiths,[5] one would have expected a much higher recovery of estrogens in pregnancy. Also unexpected was the poor conversion of estrone to estriol in pregnant women as shown in Table II, in contrast to the moderate conversion of estrone to estradiol.

TABLE II. EXTENT OF CONVERSION OF ESTRONE TO ESTRIOL AND ESTRADIOL

ESTRONE ⟶ ESTRIOL*
$\frac{\text{D content of urinary estriol}}{\text{D content of urinary estrone}} \times 100$
3.6% (Expt. 1) 3.4% ; 4.0% (Expt. 2)
ESTRONE ⟶ ESTRADIOL
$\frac{\text{D content of urinary estradiol}}{\text{D content of urinary estrone}} \times 100$
21% (Expt. 1) 28% (Expt. 2)

*The figures for the percentage conversion of estrone to estriol and the percentage recovery of the latter (Table I) happen to be about the same. This is coincidental; it is conceivable to obtain a high conversion of estrone to estriol despite a low urinary recovery of the latter. It may be pointed out, by way of comparison, that the percentage conversion of estrone to estradiol (Table II) was found to be much higher than the percentage recovery of the latter (Table I).

Summary

Experiments with isotopic estrone fail to support the views of Smith and Smith[5] particularly with respect to the influence of progesterone on the course of estrone metabolism in human pregnancy.* Our findings do not necessarily detract from the practical value of the substitutional therapy recommended by the Smiths but these findings seriously question the validity of certain biochemical theories underlying such therapy.

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*That progesterone similarly does not influence the course of estrone metabolism during the menstrual cycle is indicated in a recent report by Stimmel and Stealey.[20]

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Discussion

DR. CARL BACHMAN.—It is always stimulating to see a group of workers bring to the study of clinical problems the newer experimental techniques of the basic sciences. Drs. Pearlman and Rakoff deserve special commendation for doing so, inasmuch as the field of obstetrics-gynecology has been rather neglected in this respect. To the best of my knowledge, theirs is one of the first efforts that have been made anywhere to study the metabolism of a biologically active steroid in the human subject with the use of a tracer label.

The essayists have utilized a deuterium label to investigate the fate of estrone when that hormone is injected into pregnant women. They have found that the injected estrogen is excreted in the urine in only very small fractions of the amounts administered. The recoverable urinary estrogen is largely unchanged estrone. Apparently very little of the injected material is converted into other forms of estrogen during its passage through the body. Only a minor fraction of it is changed to estriol, that is, to the form of estrogen which, during pregnancy, is known to be the principal urinary product of the metabolism of endogenous estrogen. The fate of the major portion of the injected estrone cannot be accounted for. Presumably a part of it is excreted in the bile. The remainder must either be stored temporarily in the tissues, or else broken down into biologically inactive products and excreted as such.

As has been pointed out by the essayists, their results are not unlike those obtained by Pearlman and Pincus who, utilizing a different technique, have studied the fate of estrone injected into male subjects. Similar results have been obtained by Stimmel in nonpregnant and ovariectomized women. In view of this, it is reasonable to conclude that the fate of estrone injected into pregnant women differs very little, if at all, from that attending its injection into other adults, whether male or female.

This evening's report is unique not only because of the novelty of the investigative method employed, but also because the method chosen was so ideally suited for the purpose in view. In no other way than by the use of a radioactive or deuterium label could anyone currently hope to trace injected estrogen in a subject whose tissues, like those of the pregnant woman, are already literally saturated with endogenous estrogen. Under the circumstances, the results obtained can hardly be anything but convincing.

The importance to clinical obstetrics-gynecology of this evening's demonstration cannot, perhaps, be seen if one seeks merely for immediate practical applications. The essayists themselves modestly claim only that they have been able to find no evidence to support the Smiths' concept that the metabolism of estrone follows a different pathway during pregnancy than it does under other circumstances. But the scientific methods that Dr. Pearlman and his group have been employing are of a quality that is bound to "pay off" clinically in future, even though the direction from which results may come may not now be apparent either to us, or perhaps to the workers themselves.

DR. RAKOFF (Closing).—In answer to the question concerning the fate of the large amounts of estrogen in pregnancy, we do not know the full answer. These are the first of a series of experiments we have planned. These studies are not progressing as fast as we would like, since each experiment takes many months to complete. There is a third

experiment which has been carried out but all the results are not yet completed. The patient happened to go into labor during the time of collection of the urines and thus has given an additional approach to the study which should yield interesting results. At the moment it would seem that estriol metabolism may not be different during labor than during gestation. This does not agree with data presented by the Smiths.

If the patient mentioned by Dr. Boysen had a hepatitis, then there would be failure of complete inactivation by the liver. Studies of the metabolism of deuterated estrone in the bile would be extremely interesting.

One of the facets that interested me most about this study was the small recovery of labeled material in the urine. If estrogen is produced by the placenta in pregnant women and only relatively small amounts appear in the urine, the placenta must be producing tremendous quantities of estrogen. Indeed, the amount of estrogen production by the placenta must be really prodigious to account for the high urinary titers of late pregnancy.

In answer to Dr. Klingensmith, it is only assumed that there is a constant rate of excretion for the constant rate of metabolism which we do not know.

MALE HORMONE IN THE TREATMENT OF THE MENOPAUSE*†

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THE biologic activity of androgens in the female has been intensively studied for more than fifteen years. It has been shown that androgens inhibit the pituitary gland, inhibit ovulation, delay menstruation, and neutralize the actions of estrogens on the genital tract. Excretory studies indicate that considerable amounts of androgen, quantitatively comparable to the amounts in males, are present in the normal cyclical woman. Dingemanse, Borchardt and Laquer[29] have reported that the urine of cyclical women contained about the same quantity of comb growth promoting material as did male urine, namely 30 to 60 units per liter; and that the mean total of 17-ketosteroid content of the urine of women was 10.9 mg. for 24 hours and for men the mean value was 20.0 mg. for 24 hours.[30] Values in women ranged from 1.5 mg. to 20 mg. and in men from 9.4 mg. to 30.6 mg. These results would indicate that androgens are an important factor in the steroid sex hormone metabolism in women. Nevertheless, the exact role of androgens in women has yet to be definitely defined. Androgens have been used in the treatment of many, probably too many, clinical conditions in women and the results have not been impressive. The clinical application of androgens in women has been for the most part based on their antiestrogenic and pituitary-inhibiting action.

It is equally true that a tremendous amount of investigative work has been done on the menopause. Many of the associated hormonological and histological changes are well known, such as: the atrophic genital changes, diminished estrogen production, and increased gonadotrophic hormone excretion. Nevertheless, the exact nature and etiology of the menopausal symptoms are not clear. However, few would deny that estrogen deficiency is an important factor in the production of symptoms and that estrogen replacement is an effective means of treatment. It is difficult to reconcile this point of view with the reported successful use of male hormones in the menopause, since nearly all of the biologic actions of androgens are antiestrogenic. The theories advanced to support the use of androgens rest on somewhat tenuous grounds; and their continued use can be justified only by favorable or superior results.

*The hormones used in this study were supplied by the Schering Corporation, Bloomfield, N. J.

†Read at a meeting of the New York Obstetrical Society, Oct. 7, 1952.

Review of Literature

The earliest reference to the use of male hormones in the menopause was made in 1936 by Mocquot and Moricard[1] who noted relief of vasomotor symptoms following the administration of testosterone acetate. They also noted a state of euphoria in some patients and in others an increase of nervous instability.

In 1938 Birnberg, Kurzrock, and Livingston[2] reported the complete relief of symptoms in female x-ray castrates following treatment with testosterone propionate. McCullagh and McGurl[3] gave testosterone propionate to twelve patients with active menopausal symptoms associated with varying degrees of menorrhagia and mastalgia; and reported "striking improvement" in all. However, the hot flashes were incompletely controlled in three; one patient received estrogens as well as testosterone; and in two patients masculinizing effects necessitated discontinuation of treatment. These results show little superiority over nonspecific sedative therapy. Silberman, Radman, and Abarbanel[4] studied fifteen menopausal cases treated with parenteral and oral androgens and concluded that "the therapeutic value of testosterone propionate in the relief of the vasomotor phenomena associated with the menopause seems clearly established." This study is open to question because "appropriate sedation was prescribed when needed," and estrogens were used if arthralgias were present. Mandy and Mandy[5] noted improvement of symptoms in six menopausal patients following the use of testosterone propionate. Greenhill[6] in the 1943 Year Book recommended androgens in the treatment of the menopause in women with a history of carcinoma or endometriosis and in those women who bleed excessively following estrogens. In 1945 Gusberg[7] reported 23 of 24 patients with cancer and menopausal symptoms "strikingly benefited" by the administration of small doses of *oral* androgens; he also noted a greater permanence of results with androgens than with estrogens. In the same year Perret-Gentil[8] reported relief of menopausal symptoms in 25 patients for as long as 5 months following the subcutaneous implantation of testosterone propionate pellets. In unpublished experiments with subcutaneous implants of androgen pellets we have observed the formation of an inflammatory capsule around the implant. Within a short time absorption of hormone practically ceases as a result of the capsule formation. This effect was readily demonstrated by removal of the pellet at variable periods after implantation. The amount of hormones absorbed from such pellet implants is very small and it is doubtful if such small amounts can be clinically effective. A. A. Loeser[9] of England, who has had a large clinical experience with androgen therapy, reports that following 100 to 300 mg. of oral androgens or 50 to 100 mg. implants, all symptoms subside quickly. He adds, however, that "in the great majority of cases estrogens are superior to androgens in the control of menopausal symptoms, and androgens should be reserved for those cases where estrogens are badly tolerated and patients with cancer." Our experience with androgens in the menopause does not parallel the favorable results reported.

Procedure and Material

A total number of 62 unselected menopausal patients from the outpatient department were treated. Patients were seen once or twice weekly and vaginal smears were done at each clinic visit. All patients were judged to have menopausal symptoms by internists in the medical clinic following medical work-up. Three patients were less than 40 years of age; 23 patients were between 40 and 50 years of age; and 36 patients were between 50 and 58 years of age. Twenty-eight patients were surgical castrates; 3 were x-ray castrates and 31 were spontaneous postmenopausal women. The duration of symptoms was as follows: one year, 21 patients; two years, 13 patients; three years, 7 patients; four years, 3 patients; five years, 18 patients. All patients had stopped menstruating. No patient was treated who did not have hot flashes which we believe to be the only consistent symptom in the menopause subject to evaluation.

The symptoms varied considerably in nature and severity. The only symptom common to all were "hot flashes." Thirty-nine patients were considered to have severe symptoms (7 to 10 flashes daily) and 23 to have moderate symptoms. Other complaints recorded were nervousness, weakness, palpitation, irritability, insomnia, headache, vertigo, arthralgias, and increased sweating.

The androgens used were testosterone propionate given intramuscularly, once or twice weekly, in 25 and 50 mg. doses (52 cases); and methyl testosterone orally, once or twice daily in 10 mg. tablets (10 cases). The total dosage of testosterone propionate varied between 125 mg. and 1,500 mg. The dosage of methyl testosterone varied between 140 mg. and 1,800 mg. The duration of treatment varied from two weeks to three months with an average duration of one month.

Results of Treatment

The results of treatment were disappointing and inferior to treatment with estrogens. Approximately 27 per cent of the patients were satisfactorily relieved of symptoms and 49 per cent received no benefit (Table I). In contrast with this we have recorded 94 per cent good results with estrogen implants[10] and 89 per cent good results with stillbene derivatives[11] and 85 per cent good results with ethinyl estradiol. Nonspecific therapy has given a higher percentage of satisfactory results than we found with androgens. Thomas[31] reported 75 per cent complete or partial relief of symptoms with phenobarbital and lactose. Kovinoky[32] has obtained relief of symptoms in 62 per cent of patients with vitamin E. In none of our patients were all of the hot flashes completely eliminated. The 24 per cent of patients with partial relief in this series of cases were difficult to evaluate. They claimed some relief, which usually consisted of moderate diminution in frequency of flashes but more often the frequency remained the same but the intensity of the flashes was diminished. This is contrary to our experience with estrogen therapy; patients receiving estrogens are either satisfactorily relieved or usually the hormone is of no value. Intramuscular testosterone propionate was more effective than the orally administered methyl testosterone. No instance of a good result was obtained with oral methyl testosterone. This is difficult to reconcile with the fact that methyl testosterone is a potent androgen which acts biologically like testosterone propionate. This is also contrary to the experience with estrogens where oral therapy is as effective as intramuscular treatment.

TABLE I. RESULTS OF TREATMENT

TREATMENT	NO. OF CASES	SATISFACTORY	PARTIAL RELIEF	FAILURE
Androgens	62	27%	24%	49%
Intramuscular testosterone propionate	52	33%	25%	42%
Oral methyl testosterone	10		20%	80%
Estrogen implants[10]	124	94%		6%
Dienestrol[11]	27	89%	11%	0%
Ethinyl estradiol[12]	34	85%	12%	3%
Phenobarbital[31]	100	75%		25%
Vitamin E[32]	59	62%		38%

Cessation of treatment with androgens was usually followed by a prompt recurrence of symptoms within a few days. Many of the patients who failed to respond to androgens received relief from oral estrogen therapy; others who were partially relieved by testosterone propionate stated that estrogens were superior. The so-called "sense of well-being" reported by many investigators following the use of androgens was not observed in this group of patients. The response to androgens was rather slow, usually requiring one to two weeks.

Androgenic Side Effects of Treatment

Thirty-two per cent (16 patients of the 52 who received intramuscular testosterone propionate) developed masculinizing symptoms. The following effects were noted, in descending order of frequency: hirsutism, hoarseness, edema, increased libido, enlargement of the clitoris, and senile vaginitis.

TABLE II. RELATIONSHIP OF DOSAGE OF TESTOSTERONE PROPIONATE TO ANDROGENIC SIGNS AND SYMPTOMS

ANDROGENIC SIGNS	NO. OF CASES 16 (32%)	DOSAGE IN MG. 100-200	200-300	300-400	400-500	500-600	600-700	700-800
Hirsutism	10		2	1	1	3		3
Hoarseness	7	1		1	1	2	1	1
Edema	3	1				1	1	
Increased libido	2						1	1
Enlargement of clitoris	1						1	
Senile vaginitis	1	1						

Reference to Table II shows the relationship of androgenic signs and symptoms to the dose level. A considerable variation in sensitivity of postmenopausal women to androgens was observed. Hirsutism and hoarseness were the most easily induced virilizing signs and occurred in three patients with as little as 200 to 250 mg. of testosterone propionate. Most of the patients with toxic symptoms, however, received 400 mg. and more. Three patients developed edema. One of these patients gained 8 pounds in eleven days with a dosage of 575 mg. of testosterone propionate. Only one patient developed the complete syndrome of hirsutism, hoarseness, enlarged clitoris, and increased libido following the administration of 725 mg. of testosterone propionate. One may infer from these variations in response that the target organs, that is, skin, vocal cords, and clitoris vary considerably in sensitivity in the same patient and in different patients, with the skin and vocal cords being the most sensitive.

It has been shown in previous reports[13, 14, 15] that when testosterone propionate is administered to women who are still menstruating the critical

level of testosterone propionate is approximately 500 mg. and that below this dose level virilism is seldom induced. Furthermore, in most instances, the vaginal smear showed evidence of estrogen deficiency before the appearance of virilizing signs and could be used as an indicator to avoid overdosage. Obviously vaginal smear studies in postmenopausal women are of no value in this respect. On the contrary, we have observed hirsutism after 250 mg. of testosterone propionate given over a period of 6 weeks, without any evidence of estrogen deficiency in the vaginal smear. It would appear that the postmenopausal woman is slightly more sensitive to androgens than the younger menstruating woman as judged by the dose level of male hormone necessary to induce masculinizing signs. This is not an unexpected observation in view of the much higher level of estrogen production in menstruating women.

Effect of Androgens on the Vaginal Smear

In a previous report[15] we have shown that "if doses of 500 mg. testosterone propionate or more are given to a cyclical woman during the first 7-10 days of the cycle, the next menstrual period may be delayed from 2 to 6 weeks. During the period of amenorrhea the endometrium shows absence of the secretory phase and various stages of subnormal proliferation. The vaginal smears during this period of temporary amenorrhea in all cases show advanced degrees of estrogen deficiency indicated by the predominance of leukocytes and atrophy cells with the absence of cornified cells." Our present study would indicate that androgens have a similar antiestrogenic effect on the vaginal smear of postmenopausal women. Forty-one patients were available for study (Table III). The pretreatment smear in 26 cases consisted chiefly of normal cornified cells; in 15 cases there was clear evidence of estrogen deficiency as demonstrated by the preponderance of basal cells and leukocytes. In the latter, following doses of 100 to 800 mg. of testosterone propionate, there was no significant change in the appearance of the vaginal smears, and no evidence of any estrogenic effect. It should be noted that vaginal smear studies as applied to human beings are a qualitative test and in our hands insufficiently accurate to register varying degrees of deficiency. In one instance, Case 38, there was a change from estrogen deficiency to a full cornified effect after the administration of 300 mg. of testosterone propionate.

TABLE III. EFFECT OF TESTOSTERONE PROPIONATE ON THE VAGINAL SMEAR

BEFORE TREATMENT	NO. OF CASES	DOSAGE IN MG.							AFTER TREATMENT
		100-200	200-300	300-400	400-500	500-600	600-700	700-800	
	41								
Estrogen deficiency	15	2	3	4	1	1	3	1	Unchanged
Normal	14	3	3	3	4		1		Unchanged
Normal	12	5	4	1	1		1		Estrogen deficiency

We are inclined to interpret this result as due to either a spontaneous variation in the smear or the fact that possibly the patient was taking estrogens without our knowledge. Following doses of 100 to 700 mg. of testosterone propionate 12 patients of the 26 with normal pretreatment smears showed evidence of estrogen deficiency, whereas in 14 patients the smears were unchanged. It is interesting to note that when a state of estrogen deficiency was produced it frequently occurred with a relatively small dose (100 to 300 mg. of testosterone propionate). Here one again observes the considerable variation in sensitivity of the target organ. Two cases were of special interest

in that a change in the smears from normal to deficient, back to normal, occurred while the patients were receiving continuous treatment with testosterone propionate in total doses of 200 mg. and 550 mg., respectively. It has been claimed that androgens produce a cornifying or estrogenic effect on the menopausal smear; and this observation has been used to rationalize the use of androgens. Our findings lend no confirmation to this theory.

Effect on Endometrium

Only one patient stained during treatment with androgens. Endometrial biopsy done during the period of bleeding showed atrophy.

Comment

The following theories have been advanced to support the use of androgens in the menopause:

1. Androgens inhibit the excess gonadotrophic hormone secretion in the menopause.

2. Androgens are estrogenic in some phases of their activity and/or are converted into estrogens in the menopausal woman.

3. Androgen deficiency occurs in the menopause.

It is important to recognize the fact that androgens (testosterone propionate) are a most versatile group of hormones, which under controlled experimental conditions, usually in small animals, may simulate the biologic activity of gonadotrophins, estrogens, and progestins. For example, in the immature rat it has been shown that in short term, small dose experiments, androgens produce accelerated follicle maturation and corpora lutea.[14, 15] This is a characteristic gonadotrophic action. However, when androgens are given over a long period of time the constant effect is ovarian atrophy.[16] To apply observations obtained from such animal experiments to human beings is misleading. Let us examine the theories described above:

1. Androgens inhibit the excess gonadotrophic hormone secretion.

Increased gonadotrophic hormone excretion is a constant finding in the menopause. This increased excretion occurs as early as 3 days following castration in the human being[17] and has been considered by some to be the direct cause of menopausal symptoms. The success of androgens as well as estrogens in the treatment of the menopause has been attributed to their gonadotrophin-inhibiting action. This theory is weakened by the following considerations. Administration of large doses of gonadotrophic hormones does not produce menopausal symptoms. Physiological and pathological conditions such as pregnancy, hydatid mole, and chorionepithelioma, characterized by large amounts of circulating gonadotrophic hormones, are not accompanied by menopausal symptoms. Finally, the androgen dosage required to inhibit the hyperactive pituitary gland in the menopause greatly exceeds the therapeutic dose.

2. Androgens are estrogenic or converted to estrogens.

This theory assumes that androgens are estrogenic or are metabolized in the human being to estrogens and therefore are effective in the treatment of the menopause. Most of the evidence for this theory is drawn from controlled

animal experiments and is controversial. Butenandt and Kudszus[18] have demonstrated premature opening and cornification of the vagina in immature rats following the administration of testosterone. Similar results have been reported in castrated hypophysectomized rats. However, in adult spayed rats, androgens do not cause cornification but do prevent postcastration atrophy, by production of hypertrophy of the vaginal stroma.[19]

In some instances this hypertrophy of the vagina resembles that seen in pregnancy. Androgens in cooperation with estrogens can produce mucification of the vaginal epithelium in the rat which is a progesterone-like effect. The animal experiments on the estrogenic effects of androgens are somewhat confusing and contradictory because, in some, mucification and cornification of the vaginal epithelium are not clearly differentiated. Korenchevsky and Hall[19] have this to say: "With none of the male sexual hormones, were we able to obtain histological evidence from long duration experiments of the so-called estrogenic properties of these hormones, that is, cornification of the vaginal epithelium, though this reaction had been found by other investigators in short term experiments. On the other hand from the evidence of change in weight of the female sex organs of spayed rats and from histological studies we have been able to show that male sex hormones stimulate the development of the atrophied sex organs. Testosterone propionate increases the weight of the uterus (as judged by the weight of the cervix) nearly to normal; and the histological changes in the uterus and vagina are similar to those which were obtained during pregnancy in normal rats, though some abnormal features are seen."

It appears that the effect of androgens in castrate animals is estrogen-like in some respects but not comparable to a true estrogen. The effect of androgens on the human castrate vagina is controversial. In one human castrate, Salmon[21] reported cornification of the atrophic vaginal mucosa following the administration of testosterone propionate. This observation was confirmed by Nathanson and Towne[22] in four cases. Similar experiments in the human being by Shorr and Papanicolaou,[23] Rottermich,[24] and Abel[25] could not confirm the "so-called estrogenic effect of androgens in the human castrate vagina." In addition, all of these investigators were able to inhibit the cornifying effect of estrogens on the castrate vagina by neutralizing doses of androgens. In a subsequent study Salmon[26] reported that in order to induce cornification of the atrophic human vaginal mucosa by androgens large concentrated doses of androgens (50 to 100 mg. of testosterone propionate daily for a period of at least three weeks) were necessary. The failure of other investigators to confirm the estrogenic action of androgen was attributed by him to inadequate dosage. It is interesting to note that even with this huge dosage no proliferative effects were noted in the endometrium. At any rate, the dosage of androgens used clinically in the treatment of the menopause is insufficient to cause cornification and its reported success is unlikely to be the result of estrogenic properties.

Urinary estrogen excretion studies lend support to the theory that androgens are metabolized to estrogens in vivo. Increased urinary estrogen

excretion following the administration of androgens has been reported in normal and castrate rats,[33, 34] in normal dogs,[37] and in normal[35] and eunuchoid men.[36] However, in castrate dogs[38] there was no increase of estrogen excretion following the administration of androgens. Similarly no increase of estrogens could be demonstrated in castrate women.[38] This evidence suggests that under certain conditions androgens are converted to estrogens but it has not been proved that this conversion takes place in the menopausal woman. Even granted the above theory, that the rationale of androgens in the menopause is dependent on the conversion of androgens to estrogens, it would appear to be a most indirect and inefficient means of administering estrogens, a hormone, which advocates of androgens wish to avoid. It would be just as reasonable to use coal as fuel in a gasoline engine because gasoline can be synthesized from coal.

3. Androgen deficiency.

It has been suggested that androgen therapy is successful in the menopause because it corrects an actual deficiency. In support of this theory is the observation that there is a reduction of androgen excretion following castration in women and in the natural menopause.[28, 29] On the other hand Hamblen[27] and his co-workers have reported increased titers of 17-ketosteroid excretion in premenopausal women, x-ray castrates, and in the natural menopause.

It should be re-emphasized that in most instances androgens are antagonistic to estrogens and in only few instances do androgens simulate estrogens. It would be a rather unexpected stroke of good fortune if androgens, which for the most part are antiestrogenic, should parallel estrogen action in relieving menopausal symptoms.

The theories advanced to support the use of androgens in the menopause are not too convincing and their continued use must therefore rest on clinical results. The latter do not compare favorably with the results obtained either with estrogens or with nonspecific therapy. One can only conclude that androgens have not been proved specific in the treatment of the menopause.

The possibility exists that the favorable results reported are dependent on the metabolic effect of androgens. Androgens are known to produce retention of nitrogen, sodium, potassium chloride, creatinine, inorganic phosphorus, and water, as well as increased body weight, muscular power, and increased basal metabolic rate. These effects disappear shortly after discontinuation of the hormone. It is certainly debatable whether these transitory effects are worth while in old women in fact; a good argument could be made for the undesirability of some.

Treatment over long periods of time is frequently necessary in the menopause. The increased sensitivity of menopausal women to androgens and the high incidence of virilization which occurs with therapeutic dose levels would, per se, seem to be sufficient reason to contraindicate the use of androgens in a benign syndrome like the menopause. It has been reported[40] that following

the induction of hoarseness with androgens the vocal cords showed generalized suffused swelling with injected blood vessels; and vocal disturbances and objective changes persisted for varying periods up to two and one-half years.

As a result of the widespread, understandable though not proved, fear of carcinogenic effects of estrogens, many have turned to androgens and more recently estrogen and androgen combinations in the treatment of the menopause. We feel that this is a very undesirable trend in therapy, and that androgens should not be recommended in the menopause unless undisputed evidence is forthcoming that androgens are truly effective and specific.

Summary

1. Sixty-two menopausal patients were treated with testosterone propionate and methyl testosterone.

2. Twenty-seven per cent of these patients were relieved of symptoms.

3. Thirty-two per cent of the 52 patients who received testosterone propionate developed toxic symptoms.

4. The effect of androgens on the menopausal vaginal smear is antiestrogenic.

5. Androgens are not specific in the treatment of the menopause as judged by clinical results.

6. The theories advanced to rationalize the use of androgens are not convincing.

7. Androgens should be restricted to experimental clinics and not advocated for general use in the menopause.

I wish to express my gratitude to Dr. H. Dubrow and Dr. C. Poole for their help in the care of the patients and evaluation of the results.

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POLYETHYLENE INTUBATED SALPINGOPLASTY*†

A Newer Approach to Closed Tube Sterility

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THIS presentation is based on experimental work done during the years 1948 and 1949 on *Macacus rhesus* monkeys for the purpose of recanalizing Fallopian tubes, as well as on the subsequent clinical application of the principles found in this research. The observations made during these animal experiments were first presented to the Jefferson Society for Clinical Investigation on Nov. 12, 1949, and have been published in detail elsewhere.[1]

Not only from a review of the literature, but also from past clinical experience, it has become clear that operative procedures on occluded Fallopian tubes give consistently poor results, so much so that most gynecologists, including ourselves, have gradually discarded these operations. From a review of the literature Greenhill[4] in 1936 found that the several types of operative procedures resulted in few normal pregnancies and there were many cases of ectopic pregnancies and subsequent tubal occlusions. From the 818 operations, the results of which he had collected, Greenhill found there were 54 pregnancies, a percentage of 6.6. In 1943, Gepfert,[5] using bovine allantoic membrane in fimbriated end resection of the Fallopian tubes, was able to obtain 3 pregnancies in 28 cases in which he had performed the operation, or a successful outcome in 8.7 per cent. Snaith,[15] in 1917, reported that in 21 cases, heated by one of several procedures, 13 patients were later found to have fully patent tubes. In all the literature, we were not able to find any higher percentage than this. Among those reporting various other surgical procedures, but with little better success, are Douay,[3] Holden and Sovak,[7] Jokob,[8] Polowe,[14] and Solomons.[16]

Sterility which has been present for many years sometimes is self-cured, even late in the childbearing period, by the normal recanalization of the Fallopian tubes. Tangible evidence of this phenomenon is found in a report in the literature by Habbe,[6] in which he observed 14 late pregnancies in 75 cases of pelvic inflammatory disease resulting from gonorrhea. Approximately 19 per cent were therefore cured without any treatment whatsoever. It is also true that an occasional Fallopian tube will become recanalized even though surgically tied to produce sterility, so great is the growth tendency of

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this structure. Because of these observations we thought that a procedure might be evolved to assist the Fallopian tube in this normal tendency by means of some of the newer plastic materials which are now available.

There was indeed some past experience indicating the practicality of this principle. In 1943, Davis, Strong, and Drake[2] were able to re-establish the lumen in the ureter, both experimentally on dogs and in operations on the human being. Using an ordinary catheter, the lumen was re-established in the human ureter in cases of ureteropelvic and upper ureteral narrowing. In checking the literature, it was found that Ormand[13] in 1936 and McIver[11] in 1939 had had similar experiences. In these reported instances, the ureter healed in approximately four weeks and it was capable of normal function, both physiologically and anatomically. These workers observed no deleterious effects from the operative procedure and suggested the use of the operation in cases of ureteral obstruction.

The observations of Habbe reveal the recanalization tendency of the Fallopian tube without any treatment, and Davis, Ormand, and McIver showed by their operative procedures that the lumen of the ureter would grow over a splint. Based on the above data, experiments were conducted by us[1] to observe this phenomenon in the Fallopian tube. It was found that in some instances the tube did regenerate.

Silver wire, stainless steel wire, whalebone filament, and polyethylene tubing were used to intubate the Fallopian tube of monkeys after a gap had been made surgically.[1] It was found that the gap was restored through regeneration in each instance. The only true Fallopian tubal regeneration occurred, however, in those cases in which polyethylene tubing was used. With the other materials, the gap was found to have been repaired with fibrous tissue.

The number of cases which have been carried out on the human being since the completion of these experiments have not been many. We circularized the United States and found that 22 surgeons had done 93 operations on women. Wexler and associates[19] and Perl[12] reported true recanalization in 1951, as did Hellman.[20] Rock and Mulligan,[10] of the Free Hospital for Women in Boston, reported 77 cases in a presentation at the 1952 meeting of the American Academy of Obstetrics and Gynecology, the highest number by any one group.

Clinical Procedures

Prior to any operation, our procedure is to do a complete sterility study on both of the partners. When thorough and careful clinical evaluation of both partners has proved that the tubal factor is the only cause of the sterility, and the usual procedures do not cause reopening of the tubes, a hysterosalpingography is done to ascertain the point of stenosis of the Fallopian tubes. A preliminary course of antibiotics, 300,000 units of penicillin twice daily, is given for two days prior to operation, and for several days thereafter.

At operation, prior to the laparotomy, the cervix is dilated. After the usual vaginal preparation, and preparation of the cervix with tincture of iodine or Lugol's solution, a tenaculum is placed on the anterior lip of the cervix and left in place for subsequent manipulation.

A. Cases With Cornual End Occlusion (Fig. 1).—Following the removal of all adjacent constricting bands, two Williams intestinal clamps covered with a small piece of rubber are placed on the ovarian vessels in the region of the parametria, and two other clamps are utilized to hold the ends of the Fallopian tubes, which are excised. To minimize bleeding, a tourniquet is placed around the uterine vessels as suggested by Rubin. By the method of Meigs[9] a "fishmouth" opening is made into the distal portion of the tube, and Kelly uterine scissors are used to remove the cornual end of the uterus. The correct size of polyethylene tubing is then threaded with stainless steel wire, passed through the Fallopian tube, and attached to a probe which is passed into the uterine cavity. This is brought out through the cervix. The end of the resected Fallopian tube is then inserted into the uterine cornu, and sewed in place with sutures. The polyethylene tubing is sutured with stainless steel to the cervix, and allowed to remain for eight weeks.

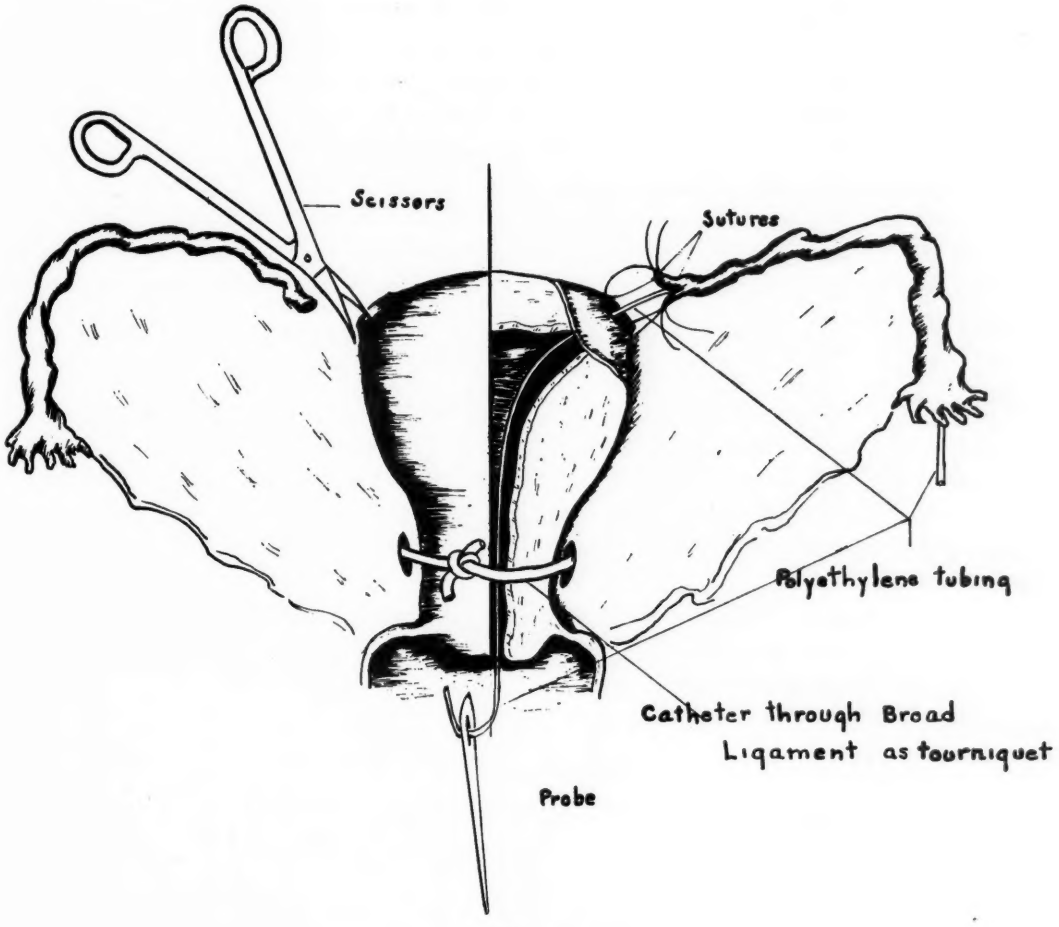


Fig. 1.

B. Occlusion at the Fimbriated Ends of the Fallopian Tube.—This is treated by use of a buttonlike arrangement made of polyethylene tubing which was devised by Rock and Mulligan, and further

refined as an umbrella-like structure. After the ostium has been opened, the umbrella-like structure of polyethylene tubing, as shown in Fig. 2, is sewed to the fimbriated end with sutures in such a way as to hold it in place. This mold in the fimbriated end is left in place for a period of eight weeks; its removal is later accomplished by a second abdominal operation.

C. Mid-portion of the Tube.—For the recanalization of tubes which have been tied in the mid-portion, the procedure is shown in Fig. 3. Polyethylene tubing of correct size is placed in the gap, and the tube is allowed to grow over this area. No attempt is made at securing the ends together. A long loop of tubing is allowed to remain free, sewn to the anterior sheath of the abdominal fascia, and subsequently removed under local anesthesia in eight weeks. Any needed surgery, such as releasing of adhesions, resection of polycystic ovaries, and the treatment of any other pathological pelvic findings is attended to in the usual manner.

Weisman[18] has shown that the rapidity of human Fallopian tube healing was the apparent cause of the poor results in tubal surgery, prior to the use of polyethylene tubing as a splinting material. He found that regeneration of reconstructed Fallopian tubes occurred within 24 hours, and suggests that the Rubin test be done within a few days after the operation, and repeated at frequent intervals. Since we leave the polyethylene tubing in place for eight weeks, insuring the patency of the Fallopian tubes for that length of time, we do our first Rubin test a few days after the removal of the polyethylene tubing, and at subsequent monthly intervals, immediately following each period.

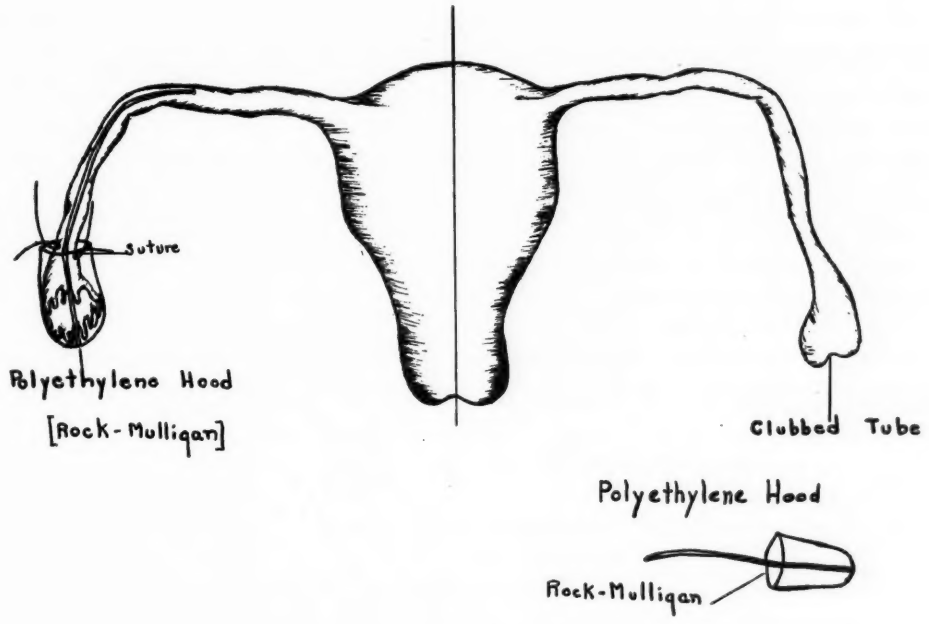
Analysis of Results of Procedure

We circularized the members of the American Board of Obstetrics and Gynecology and obtained reports from the persons listed in Table I. The results obtained in this series of cases are reported in Table II. From the reports received from our questionnaire, certain information may be noted in regard to the techniques being used, and the results being obtained.

TABLE I. SOURCE OF CASES REPORTED IN ANSWER TO QUESTIONNAIRE

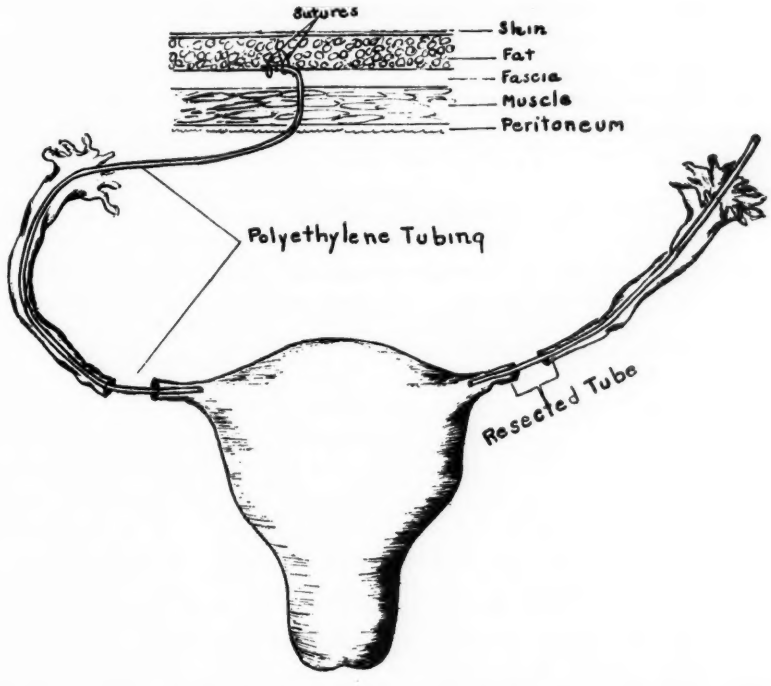
S. Leon Isreal	3	Raymond L. Young	4
Robert B. Greenblatt	3	Ernest W. Page	3
Robert N. Rutherford	5	William C. Weir	4
T. H. Cremo	1	John C. Weed	2
John R. Gepfert	7	Charles Potter	2
V. S. Counseller	1	C. W. Seibert	2
L. E. Bauer	1	Wesley I. Pommerenke	28
S. B. Lovelady and C. L. Liggett	2	C. T. Beechman	2
E. O. Strassman	2	Louis L. Friedman	7
Norman Hernig	1	Authors' cases	9
C. M. Gill	4		
		Total	93

The tubing was allowed to remain in situ for periods varying from four days to two months, in the majority of cases for less than two weeks. It should, in our opinion, remain in situ for at least two months, but only five



SCHEMATIC OPERATIVE TECHNIQUE FOR FIMBRIATED END OCCLUSION USING POLYETHYLENE HOOD AND TUBING (ROCK-MULLIGAN)

Fig. 2.



SCHEMATIC OPERATIVE TECHNIQUE FOR TUBAL OCCLUSIONS BETWEEN FIMBRIA AND CORNU USING POLYETHYLENE TUBING

Fig. 3.

of our informants allowed it to remain that long. The antibiotics used ranged from penicillin to terramycin and included combinations of penicillin with streptomycin, and penicillin with sulfadiazine. Antibiotics were usually given preoperatively and continued for three to five days postoperatively. Approximately 30 per cent of the patients were given no antibiotics. With regard to the results, the two miscarriages apparently had no relation to operative work on mid-tubes. Most of the operators stated that it was still too early to report on pregnancies as most of the operations had been done in the past month to one year.

TABLE II. NINETY-THREE OPERATIONS BY TWENTY-TWO OPERATORS UP TO NOVEMBER, 1952

TYPE OF OPERATION		OPEN TUBES		PREGNANCIES	
Fimbria	23	2	(8.7%)	1	(50 %)
Cornua	44	23	(52 %)	2	(8.7%)
Mid-tube	26	13	(50 %)	3	(23 %)
Not indicated		18		13	(72 %)
Total	93	56	(65%)	19*	(34 % of patients with open tubes) (20 % of patients operated upon)

*Among these pregnancies two ended in miscarriage and one was an ectopic pregnancy.

The figures reported by Drs. Rock and Mulligan, not as yet published but given before the American Academy of Obstetrics and Gynecology in December, 1952, are shown in Table III.

TABLE III. RESULTS OF OPERATIONS PERFORMED BY ROCK AND MULLIGAN JAN. 6, 1949, TO SEPTEMBER, 1952

TYPE OF OPERATION		OPEN TUBES		PREGNANCIES	
Cornua	53	20	(37.7%)	5	(25%)
Fimbria	24	15	(62.5%)	5	(33%)
Total	77	35	(45.4%)	10*	(29% of patients with open tubes) (13% of patients operated upon)

*Among these pregnancies there were two ectopic pregnancies and one miscarriage.

A combination of our collected figures with the reported results of Rock and Mulligan indicates (Table IV) that there have been 170 operations of this type performed with a total of 29 pregnancies.

TABLE IV. RESULTS IN ALL CASES FOR WHICH REPORTS ARE NOW AVAILABLE

Total	170	91 open tubes (53.5%)	29 Pregnancies 32% of patients with open tubes 17% of patients operated upon

Summary

Reports seem to support the premise that a bridging material may be used in recanalization operations on Fallopian tubes in women.

Polyethylene tubing has proved to be innocuous in the human being as well as in the tissues of experimental animals.

A reported cure rate several times as great as was possible heretofore (6.6 per cent of Greenhill's cases as against 17 per cent in this series) is

apparently possible with intubated salpingoplasties with the use of an innocuous bridging material in tubal occlusion.

The number of cases reported is still not sufficient to take this method out of the experimental stages.

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Discussion

DR. J. ROBERT WILLSON.—The methods of treatment of the woman whose tubes are occluded leaves much to be desired but utilization of the principles outlined in this paper may in the future improve the results. The fact that in the collected series only 34 per cent of the tubes remained open after operation, while in Rock and Mulligan's personal patients 60 per cent were patent, suggests that experience and the development of a planned program for postoperative management are of importance in determining the end result.

The relatively low pregnancy rate in patients whose tubes are patent postoperatively should not be too discouraging because at best the results will be far from perfect. In some instances too short a time has elapsed since the operation for pregnancy to occur, while in others the lesion might not have been suitable for correction. It would be of interest to know of the findings at operation in those patients in whom infertility persisted despite the establishment of tubal patency since the selection of patients for operation plays an important part in the end result. Little can be expected in the patient in whom each tube is replaced by a huge hydrosalpinx, in those in whom there are extensive bowel adhesions which may re-form and separate the tubal ostium from the ovary, or in the patient in whom the disease is so extensive that the sacrifice of the adnexa on one side is necessary. The most suitable candidates should be those in whom pathologic changes in the tubes and pelvic adhesions are minimal and in whom the reproductive processes otherwise are normal. Even in such ideal patients the ultimate success probably would be less than perfect since infertility even in the absence of demonstrable abnormality cannot always be corrected.

The change in tubal function due to the operation may preclude pregnancy even though patency is restored. Sufficient time is necessary after fertilization of the ovum for it to develop to a point at which it can implant in the endometrium; this ordinarily takes place as the ovum descends through the tube. If the operation shortens the tube too much the fertilized ovum may traverse it so rapidly that it is not ready to implant properly

when it reaches the uterus and thus will be lost. This is most likely to occur in cornual closures in which it is necessary both to resect a portion of tube and to sacrifice more in pulling it through the uterine wall. In the future, I intend to attempt to prevent this abnormal shortening by bringing the tube to but not through the uterine cornu over the polyethylene tubing. The authors' suggestion that no attempt be made to close a resected defect in the middle of the tube would accomplish the same purpose in occlusions in this area.

If the patients for tubal plastic procedures are properly selected, and if the authors' suggestions are carefully followed, the operation should provide an opportunity for pregnancy for many women who otherwise might remain sterile.

DR. CASTALLO (Closing).—The operation I have described is not an easy one. It is time consuming, and technically difficult. The operation should be done as a last resort, after all other procedures have been attempted for opening the closed Fallopian tubes.

The work is still in its experimental stages. I hope that the original work will stimulate in others an interest in some type of tubal operative procedure which will give better results than have been obtained in previous years. Even though open tubes do not necessarily mean procreation, a patient with open tubes has much more of a chance of becoming pregnant than one with the tubes completely closed.

The only time that the polyethylene tubing is passed into the uterine cavity, is in these cases in which we do a cornual resection. It is impossible, in most instances, to pass polyethylene tubing through the cornual end of a tube without resecting it. When the "button" and "umbrella" method is used, the apparatus is removed after two months by re-entering the peritoneal cavity.

It was our impression that Dr. Rock's figures, as we quoted them, included only the cases which have been done with polyethylene tubing alone, and which have been followed. They do not include other types of procedures.

Polyethylene tubing, as we use it, comes in many sizes. The size we use most is that which will pass through a 16 or 18 gauge needle easily.

SIMPLIFIED METHOD FOR STERILIZATION OF THE FEMALE

TOMMY N. EVANS, M.D., ANN ARBOR, MICH.

(From the Department of Obstetrics and Gynecology, University of Michigan)

ABSENCE of a single satisfactory method of sterilization of the female is apparent from the large number of operative procedures in current use. Although in most instances individual procedures used in the past have in their design certain merit, none has proved to be without significant fault.

Chief among the qualities desired in a method of sterilization are: (1) effectiveness, (2) technical simplicity, (3) brief operative time, (4) minimal blood loss, (5) low risk to the patient, and (6), in some instances, reversability.

In an effort to incorporate these qualities in a single procedure, the following method was designed. A forceps 9 inches in length grooved to hold a tantalum clip was used (Fig. 1, *A*). Each clip is 0.025 inches thick, 1 inch long, and 3/32 of an inch wide (Fig. 1, *B*). After the pelvis is entered, each Fallopian tube is suspended with Babcock clamps, and a single clip is placed at the junction of the ampulla and infundibulum of each tube. At this point the muscular coat is thin and the lumen is only about 2 mm. in diameter and thus easily occluded. The muscular wall of the tube is firmest and thickest in the isthmic portion, somewhat less in the ampulla and thin and relaxed in the infundibulum. Multiple horizontal grooves on the inner surface of the clip grasp the tissue firmly. Compression of the curved clip (Fig. 1, *C*) approximates the ends first so that added pressure does not result in the escape of tissue from the open end as may occur from closure with an angulated clip (Fig. 1, *D*).

The clip extends just into the mesosalpinx so that there is no interference with ovarian blood supply. The spring joint (Fig. 1, *a*) limits closure of the instrument, obviating excessive compression and damage of the tube but permitting adequate occlusion. Mistaken application of the clip to the round ligament is improbable since the tubal end must be identified before a clip can be placed adjacent to it.

While the effectiveness of any technique for sterilization can be established only after extensive application and later evaluation, in our hands the procedure described above has already demonstrated its (1) simplicity, (2) safety, (3) bloodlessness, and (4) time-saving qualities. Its technical simplicity is obvious and it entails no blood loss. The operative time is short and practically negligible when the tubal occlusion is done in conjunction with laparotomy for another procedure. These features are especially desirable when the indication for sterilization is a systemic disease which makes the patient both a poor pregnancy and operative risk. Here the time-saving feature, bloodness-

ness, and minimal operative manipulation may be of major importance. Absence of added blood loss is of particular advantage when sterilization is done at time of cesarean section or in the postpartum patient in whom troublesome bleeding is occasionally encountered.

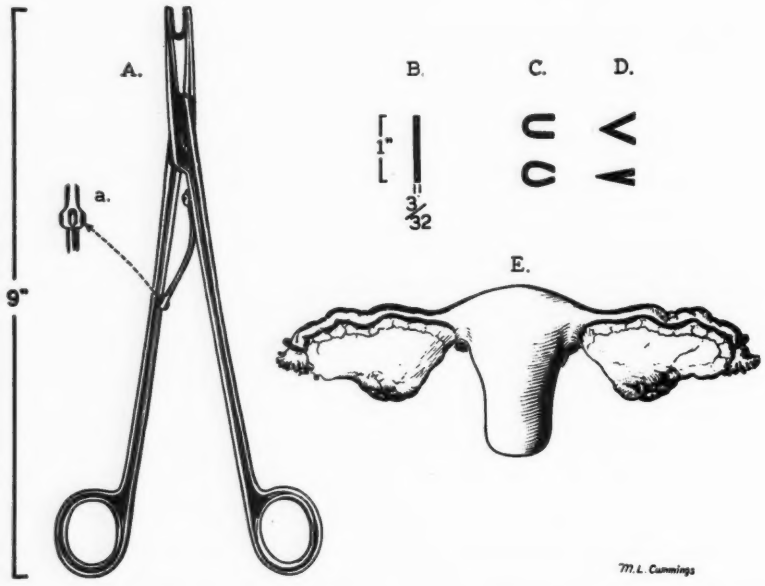

Fig. 1.—*A*, Clip forceps with clip in place; *B*, unbent clip with horizontal grooves; *C*, lateral view of curved and *D*, sharply angulated clip; *E*, diagram showing points of occlusion with clips.

When the original indication for sterilization no longer obtains, reversability of the procedure without sacrificing its effectiveness is desirable. At this stage of our experience it is speculative as to whether or not this technique will permit subsequent restoration of reproductive function. However, there are several points favoring its reversability. As demonstrated in Fig. 1, *E*, more than 90 per cent of normal Fallopian tube remains intact proximal to the point of occlusion. Also, there is less anatomical distortion of the tubovarian relationship than with most sterilization methods now in use. Since the clips are made of an inert metal, no inflammatory reaction will occur on this basis. Damage to the tube is minimal, but to effect occlusion there must be some compression and consequent tissue damage leading to fibrosis. The clip is placed so that tubal occlusion is assured, but it should not extend into the mesosalpinx to the point where ischemia of adjacent tissue is produced.

At this point there is no apparent contraindication to utilizing this procedure in all women in whom sterilization is advisable. Brevity of the operation, absence of blood loss, and technical simplicity reduce the risk to the patient, particularly when it is done under local anesthesia on those who have a serious illness contraindicating pregnancy. Furthermore, the long shank of the clip forceps facilitates sterilization from the vaginal approach, especially when done in conjunction with a plastic repair.

Summary

A method of sterilization of women is described which offers technical simplicity, minimal operative time, reduced risk to the patient, absence of blood loss, and possibly reversability. More extensive use of the procedure is essential to assess its value. It is hoped that the idea will appeal to others to the point where they will try the method and aid in its evaluation.*

*Equipment available from Randolph Surgical Supply Co., 60 Columbia Street, West, Detroit 1, Mich.

THE EFFECT OF A NEW POTENT UTERINE RELAXING FACTOR OF THE CORPUS LUTEUM IN THE TREATMENT OF DYSMENORRHEA*

GEORGE H. REZEK, M.D., CICERO, ILL.

THE purpose of this paper is to report the favorable results secured in a series of clinical cases of dysmenorrhea with a new, nonsteroid, water-soluble uterine relaxing factor† obtained from the corpus luteum.

In 1942[1] we published the results of a clinical study of the value of Lutein in 650 cases of threatened and habitual abortion and other obstetrical complications involving the necessity of inhibiting uterine contractions. The favorable results obtained were shown to be due to the effectiveness of this product in inhibiting uterine contractions, as demonstrated by the intrauterine bag method of Moir.[2] When 10 c.c. of aqueous Lutein were injected into a patient whose uterine contractions had been stimulated by 1 c.c. of Pituitrin, there was complete cessation of contractions within twenty-five minutes. It was apparent from our study that this inhibition of contraction was not due to the progesterone content of the solution, and we suspected the presence of a heretofore unidentified substance. We drew attention also to the imperative need of further investigation of corpus luteum derivatives to determine the reason for the results which we had secured.

At that time there was no satisfactory laboratory method of standardizing substances derived from the corpus luteum except in terms of progesterone, which, in our experience, does not produce uterine relaxation. An intensive investigation, undertaken to devise a laboratory method of assaying the potency of these substances in terms of such relaxation, culminated in the development of a new technique for the determination of their effect on uterine activity, which was published by Krantz, Bryant, and Carr[3] in 1950.

New Uterine Relaxing Factor Assay

The new method of assay is based on the development and maintenance in the test animal of a uniform endocrine picture. This state was induced artificially in guinea pigs by injections of estrogenic material. One-tenth mg. of Diovocylin injected subcutaneously into each animal daily for seven to twelve days before use caused proliferation of the uterus approximately equal to that of a twenty-day pregnancy. In the conduct of the assay, the uterus is exposed through a midline abdominal incision, this organ then being attached to the writing lever of a kymograph. The jugular vein is also exposed for the purpose of making injections and the effect of such injections on uterine motility is observed by means of kymographic tracings.

*Presented at a meeting of the Chicago Gynecological Society, Jan. 16, 1953.
†Supplied by Hynson, Westcott & Dunning, Inc., Baltimore 1, Md.

A total of 26 different substances, including progesterone, were used with the idea of defining the specificity of the new factor in inhibiting uterine contractions. It was found that of these substances only the new uterine relaxing factor was effective. The test is, therefore, highly specific for this substance and is so extremely sensitive that 0.002 mg. produces definite relaxation.

The degree of relaxation of uterine contraction thus provides a direct method of assay of the potency of different samples of material obtained from the corpus luteum. Various methods of increasing this potency were devised and finally a highly active water-soluble nonsteroid substance was developed which inhibited uterine contractions when given by mouth as well as by injection.

A laboratory investigation reported by Hisaw and Frieden[4] at the Laurentian Conference on Hormones in Canada, September, 1952, establishes the fact that the uterine relaxing factor is a protein type of compound. It is interesting to note that still another ovarian substance was described by these investigators and their associates[5] at Harvard some years ago. This substance, which they have named relaxin, is closely related to the new uterine relaxing factor, but differs from it in that relaxin has the property of relaxing the symphysis pubis of the guinea pig. Further evidence that the two substances are not identical is provided by their electrophoresis curves.[6]

The effectiveness of the uterine relaxing factor in threatened and habitual abortion will be the subject of another paper.

Clinical Results

In view of the probable relationship between uterine contractions and dysmenorrhea, it was decided to try the new potent substance orally in a series of clinical cases. This investigation was undertaken more than two years ago and to date a total of 298 patients have been treated with highly satisfactory results. Seventy-two patients who responded well but who had also used a sedative were ruled out of this report.

For the purpose of clarity the clinical results will be divided into two series, the first treated by the original dosage schedule, and the second by a revised schedule.

First Series.—

Seventy-three patients with a hyperplastic endometrium immediately before menstruation who used the new substance alone experienced relief from their cramps. Forty of these obtained excellent relief with 150 or 300 units every four hours. In this series the patients were observed for at least six periods and in some for as many as eleven periods. All were free from cramps and able to continue their daily routine, which they had been unable to do before use of the drug. Table I shows the number of periods observed in each of these cases.

TABLE I. NUMBER OF PERIODS OBSERVED

11 periods	4 patients
10 periods	6 patients
9 periods	15 patients
8 periods	5 patients
7 periods	5 patients
6 periods	5 patients

In another 20 cases the results can be described as good, in that patients were definitely better but did experience a few mild cramps. Each of these patients was observbed for at least six periods. Fair results were obtained in 10 other cases. In this group the patients reported definite improvement but were still aware of menstrual cramps with some degree of pain. Only 3 stated that they had obtained no relief from the drug.

As a means of determining the elapsed time between the administration of the drug and relief of pain, 15 patients in the "excellent group" were asked to present themselves while having cramps and were given 450 units at once. Thirteen stated that within 15 minutes the cramps had almost completely disappeared. The other 2 had some improvement with the first dose and almost complete relief when an additional 300 units were given three hours later.

Representative Case Histories.—

C. R., aged 23 years, had had dysmenorrhea every month since she was 13 years old. She had had over a period of 8 years, as she stated it, "all types of endocrine therapy." A dilatation and curettement and finally a presacral sympathectomy were carried out without relief of her menstrual cramps. This patient experienced relief from the uterine relaxing substance if she was able to take it before menstrual nausea and vomiting set in. When the period started at night and she began vomiting, she was unable to take tablets, but if the period began during the day and tablets were taken in time she received complete relief from her uterine cramps.

R. R., aged 28 years, had had dysmenorrhea since the birth of her second baby 4 years ago. Excellent results were experienced with 150 units every 4 hours.

K. D., aged 19 years, had had cramps since the onset of the menses at the age of 14 years. No previous therapy had been used, but she reported excellent results with 150 units every 4 hours.

M. P., aged 16 years, was a virgin and no endometrial biopsy was performed. She had had cramps since the onset of the menses at the age of 12, but received excellent results with 300 units evry 4 hours. Rectal examination revealed no pelvic pathology.

A. B., aged 19 years, had had dysmenorrhea for the past 4 years. The menses started at the age of 13 and the first 2 years were pain free. There was no pelvic pathology. She received excellent results with 150 units every 4 hours.

R. H., aged 33 years, was a nullipara. The menses started at the age of 14 years; the first 10 years were without dysmenorrhea, but during the last 9 years, she has had severe dysmenorrhea. Pelvic examination revealed the patient to have bilateral salpingitis. Three hundred units of the drug every 4 hours gave excellent results in relieving cramps.

In the group with hypoplastic endometrium immediately premenstrually there were 10 patients; only 2 claimed some relief and 8 said they experienced no relief.

Second Series.—

It was our impression at this time that, in general, patients responded more rapidly to the larger doses. In some instances relief with dosages up to 450 units was not secured until the second, third, or fourth dose. We had seen no evidence whatsoever of untoward reaction and, in view of the fact that other investigators had used much larger doses experimentally, we decided to give an initial dose of 1,500 to 3,000 units. Patients in the second series received an average of 2,300 units initially. With this regimen we found that relief of pain was secured within approximately 15 minutes. Furthermore, in some cases only one dose was required for any given period.

Fifty-eight patients with normal endometrium were treated in this way and of these 40 experienced complete relief of pain within fifteen minutes. Of 10 other patients with hypoplastic endometrium 3 experienced relief with

a dose of 3,000 units. It is apparent, therefore, that the larger dosage is more effective and that patients with a normal endometrium respond more readily and frequently than those with a hypoplastic endometrium. In this series patients were observed for at least three periods.

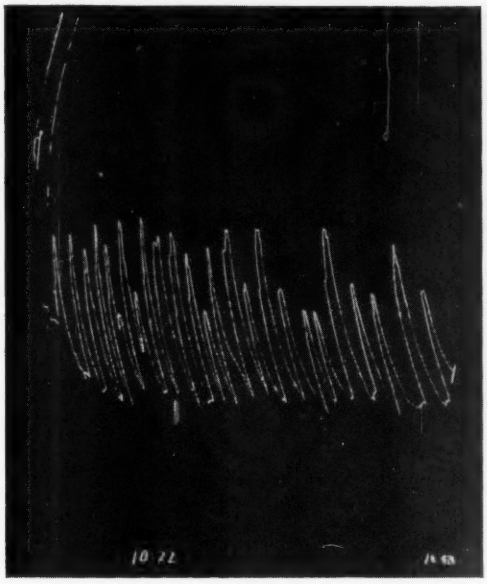

Fig. 1.—One c.c. of normal blood serum was injected into the jugular vein of a previously prepared guinea pig after definite rhythmic contractions had been established at 10:22. No effect was noted on the kymographic tracing.

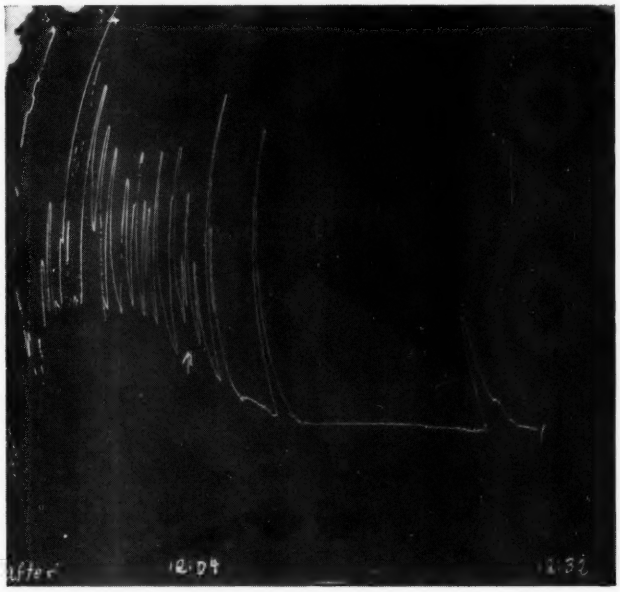

Fig. 2.—One c.c. of serum taken from a blood specimen of the patient in Fig. 1 was injected into the jugular vein of a previously prepared guinea pig at 12.04. The specimen was drawn one-half hour after the patient had taken orally 900 units of the new, nonsteroid, water-soluble uterus-relaxing factor. Cessation of contractions was noted in four minutes.

A further observation in this series was that in a number of instances patients who suffered regularly from painful periods experienced no such symptoms for several periods following the use of 3,000 units of the uterine relaxing factor. The number of patients reporting relief for more than one period following a single large dose is not, however, sufficiently large to permit any definite conclusions.

Laboratory Confirmation

Since the guinea pig uterus relaxation test had been found to be highly specific for the new substance, it was decided, as an additional check on the absorption of the drug, to take blood samples from patients who had received it and to test them by the above method. As a control, samples of the patients' blood were also taken before administration of the drug. It was found that, although control samples produced no effect in inhibiting uterine contractions, specimens taken thirty minutes after administration produced a characteristic relaxation of the guinea pig uterus. This is illustrated in Figs. 1 and 2 which are reproductions of typical kymographic tracings secured before and after administration of the uterine relaxing factor in a total of 25 patients to date.

Summary

1. The highly favorable results in a series of 298 clinical cases of dysmenorrhea treated with a new potent uterine relaxing factor of the corpus luteum are described.

2. Complete relief was secured within fifteen minutes in approximately 70 per cent of patients with normal endometrium when treated with an initial dose of 3,000 units.

3. Response to the smaller initial dose used in the first series was not quite as satisfactory, demonstrating the need of a large first dose.

4. Patients with a hypoplastic endometrium appeared to respond less well.

5. No undesirable by-effects of any kind were noticed, although some patients were observed for as long as 11 periods.

6. All patients who responded were able to continue their daily routine, which they had previously been unable to do.

7. The suggested dosage for the new uterine relaxing factor is 1,500 to 3,000 units at the beginning of pain. In many cases no further drug is required for that period.

8. Absorption of the drug into the blood stream was confirmed by laboratory procedures.

Conclusion

In our experience the new uterine relaxing factor described above is effective in the relief of menstrual pain.

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Discussion

DR. HUGO C. BAUM.—The thesis of the essayist is that dysmenorrhea is the result of increased tonus of the uterine muscle and that by relieving this tension with a specific relaxing factor of the corpus luteum, dysmenorrheic patients can be freed from their annoying symptoms.

I assume that he is referring to the tests made by Krantz, Bryant, and Carr. If I am correct, the article has been misquoted. They did test 26 substances but on the excised uteri from pregnant mice and not on the uterine horns of guinea pigs. Of the 26 substances tested, 15 caused relaxation. It is interesting to note that they found 0.5 per cent atropine sulfate caused uterine tension. They concluded that the excised muscle test was unreliable, and then devised the technique of using the guinea pig uterus in vivo as described. They confirmed the work of Hisaw and his associates "that aqueous corpus luteum extracts contain an active principle which when carried to the uterus via the circulation causes a diminution in uterine activity and tonus." This is a minor point but there is enough confusion in the literature so that one should be careful in quoting references.

Judging from the cases cited by the essayist the new substance is not only effective in the treatment of primary but also some cases of secondary or acquired dysmenorrhea. Reynolds in surveying the literature states, "Arrhythmic contractions of extreme intensity and duration are found only in association with ovulatory cycles and the sine qua non for painful menstruation is an ovulatory cycle." Dr. Rezek found that this group, the patients with normal endometrium, responded most favorably to the new hormone. Why do patients whose ovaries have formed corpora lutea and should be producing their own relaxing hormone have increased uterine muscle tone and dysmenorrhea? Why should they respond most favorably to this new hormone? Patients with dysmenorrhea who have ovulation suppressed with estrogens usually have painless withdrawal bleeding. One must conclude that the corpus luteum produces not only a relaxing factor but also an exciting factor. Possibly an imbalance between these two substances is a cause of dysmenorrhea. Has the essayist tested the serum of normally menstruating individuals who do not suffer from dysmenorrhea for the presence of a relaxing substance? Why did not the serum of the dysmenorrheic patients cause increased muscle tone in the guinea pig uterus? These are questions without answers at the present time.

The results obtained by the use of this hormone are excellent. The author reports upon 298 patients; 72 responded well but were eliminated from this report because they had used sedation; thus the report is on 226 patients. In the first series results of treatment in 83 cases and in the second series of 68 cases are reported, totaling 151 cases. What about the other 75 cases of which no mention is made?

I would like to conclude my discussion by quoting the preface of an article of which the essayist was co-author, "A healthy skepticism prevails concerning new remedies which prevents their wholesale adoption until thoroughly tested."

DR. JAMES BRADBURY, Iowa City, Iowa.—I would like to inquire whether this substance has been tested for the relaxin content by using relaxin tests. There may be two substances and I would like to know whether there is a relaxing agent contained in both. The question is whether this is the relaxin factor as described by Hisaw or a different one.

DR. REZEK (Closing).—In answer to Dr. Baum, I was not quoting the article of Krantz, Bryant, and Carr, but relating my own experiences with various drugs and hormones on the previously prepared uterus in situ. Dr. Baum's remarks refer to the first page of the article by Krantz, Bryant, and Carr in which they refer to the use of the excised uterus. The results differ greatly when one uses the uterus in situ.

The active relaxing factor of the corpus luteum described in this paper has never been, as far as I know, isolated chemically nor synthesized.

In answer to Dr. Bradbury, the relaxing factor of Hisaw is different from this new nonsteroid, water-soluble uterine factor as shown by the electrophoresis curve.

Seventy-five cases were included in the total but not definitely reported and in these 75 cases satisfactory results were obtained in at least three periods.

The blood serum of the menstruating, nondysmenorrheic woman was tested without any definite effect on the previously prepared guinea pig uterus. However, not enough of this work has been done to come to definite conclusions, this having been tested on only one guinea pig.

PREGNANCY ASSOCIATED WITH MULTIPLE SCLEROSIS

A Report of Three Cases

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CAPTAIN JOHN W. O'GRADY, MEDICAL CORPS, UNITED STATES ARMY**

THE occurrence of pregnancy in patients with multiple sclerosis is uncommon. Several large series have been reported in the German literature,[1, 2, 3, 4] but only a few well-studied cases have been reported in this country.[2, 6, 7] In our experience several instances of pregnancy associated with multiple sclerosis have been encountered and three representative cases are herein reported.

CASE 1.—A 32-year-old white woman, gravida iii, para i, abortio i, was admitted to Walter Reed Army Hospital on June 14, 1947, with a history of multiple sclerosis of ten years' duration. Twelve years prior to admission she delivered, without complications, a full-term infant. A therapeutic abortion was performed in 1940 because of multiple sclerosis.

Prior to the 1947 admission, the multiple sclerosis had been considered static for about two years. However, on admission the disease was found active and far advanced and complete neurological and medical studies were made.

Physical examination revealed a well-developed thin white woman, 32 years of age, with a blood pressure of 120/80. A pelvic examination revealed a symmetrically enlarged uterus consistent in size with an eight weeks' pregnancy. Biceps reflexes were present and normal, but patellar and abdominal reflexes were absent. The Babinski reflex was positive bilaterally. There was marked bilateral past pointing. The Romberg test was positive and the scanning of speech was well advanced. An admission diagnosis of multiple sclerosis, moderately advanced, and pregnancy of eight weeks' duration was made.

Shortly after admission, medical consultation was obtained. The consultant agreed with the diagnosis and felt that the disease was far advanced. He suggested a therapeutic abortion and tubal ligation. A civilian neurological consultant examined the patient, reviewed her records, and agreed with the diagnosis and plan for therapy.

Routine laboratory studies were found to be within normal limits, and, on June 25, 1947, under general anesthesia, a therapeutic abortion, dilatation and curettage of the uterus, and ligation of the Fallopian tubes through a small Pfannenstiel incision were performed. She was given Ergotrate three times daily for three days following the operation. Skin sutures were removed on the fifth postoperative day and the patient was discharged on July 5, 1947.

CASE 2.—A 23-year-old white primigravida first noticed symptoms referable to her condition in June, 1945, at which time she became aware of a numbness in the left leg and an ill-defined paresthesia of the hands. These symptoms lasted approximately one month.

Her past history was essentially noncontributory, but her family history was significantly interesting. Her mother was said to have had multiple sclerosis and two uncles were similarly affected at the time the patient was admitted.

This case was followed indirectly from June, 1945, nearly two years prior to this pregnancy, until six months post partum.

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In June, 1945, the patient, then 21 and unmarried, complained of a "dead feeling" in her left leg, and physical examination revealed an exaggerated left knee jerk and a doubtful plantar reflex.

Two weeks later the leg had improved, but the patient then experienced a similar sensation in the fingers. In October, 1946, a general premarital examination was made, and the following significant findings noted: slight hyperesthesia to pin prick in the area corresponding to the distribution of the first two divisions of the trigeminal nerve on the left. All reflexes were normal with the exception of the plantars which were hyperactive.

The patient was married to an American soldier in October, 1946, and in November of the same year she experienced difficulty with vision. Her doctor made a final note in February, 1947, to the effect that all neurological findings were normal.

In March, 1947, the patient joined her husband in Germany, and two months later she noticed a progressive difficulty in walking. She was hospitalized for two months, and discharged as improved.

In September, 1947, when she was five months pregnant (expected date of confinement, mid-January, 1948), she noticed increasing fatigue and weakness in the legs. She could no longer stand alone, and had difficulty in controlling urination to the point of incontinence. Vision in the right eye became poor, and she complained of numbness and tingling in the hands and arms. Weakness in the lower extremities progressed to paralysis and her speech became scanning in character.

She was brought to the United States on Nov. 9, 1947, and an examination revealed a nystagmus, bilateral hypoactivity of the biceps reflexes, hyperactive triceps reflex on the right and hypoactive on the left; knee jerks and ankle jerks hyperactive bilaterally, and abdominal reflexes absent; positive Hoffmann sign on the right and bilaterally positive Babinski and Chaddock's signs. The right leg was paralyzed and the left very weak. Both arms were extremely weak, and there was atrophy of the muscles of the right hand. Incoordination and ataxia were noted in the finger-to-finger, and finger-to-nose tests, and there was coarse tremor of the outstretched hands. Proprioceptive sensation in the arms was impaired, and there were scattered areas of hyperesthesia over the neck and upper chest, but hypesthesia over the rest of the body.

The laboratory report was: urinalysis, negative; red blood count, 3.7 million; hemoglobin, 11.5 Gm.; blood type, Rh positive; blood urea nitrogen and Van den Bergh tests, normal; Kahn test, negative; prothrombin time, normal; vaginal smear, *Monilia albicans*. The x-ray report showed a normal chest and an adequate gynecoid pelvis.

When first seen in the Obstetrical Section, the patient gave the impression of a preterminal stage of paralysis. A neurological consultant and an obstetrical consultant concurred in the opinion that the patient presented the typical picture of a case of "multiple sclerosis, apparently aggravated by pregnancy." Because of her grave condition, it was felt that interruption of pregnancy by cesarean section would have been fatal.

In the following week her general condition rapidly deteriorated. She became sluggish, her temperature rose to 103° F., and extraocular palsies developed. A medical induction was attempted but without success. Two days later the patient had a chill. Her temperature increased. The urine became cloudy and a culture revealed *Escherichia coli* and *Streptococcus fecalis*. Therapy, with increased parenteral fluids and penicillin, was started immediately, and a gradual decrease in temperature was noted during the following three days. Concomitant with the improvement in temperature and urinary tract infection, there was a slight but definite general improvement. In the following two weeks a slow but definite remission in the neurological condition was noted. The patient was noticeably improved by the time of the spontaneous onset of labor, Jan. 13, 1948.

Delivery of a normal full-term female infant was effected by low forceps with the utilization of a left mediolateral episiotomy. Sedation was unnecessary, as labor was relatively painless, and one hour prior to delivery she was given 50 mg. of Demerol. The episiotomy and low forceps delivery were accomplished with pudenal block anesthesia produced by 1 per cent procaine.

Laboratory studies made during her stay at this hospital were within normal limits with the exception of a persistently lowered serum protein and an occasional trace of albumin in the urine.

From the obstetrical standpoint, her postpartum course was uneventful except for a low-grade fever ascribed to the subsiding urinary tract infection.

On Jan. 30, 1948, the patient was again seen by the neurologist and marked improvement was noted. There was moderate weakness of both arms and legs, but there was movement in all the extremities including the toes; ataxia had diminished considerably, and the finger-to-nose test was nearly normal. There was a slowing of all fine movements of both hands; sensation had cleared considerably, hypesthesia and hypalgesia existed below the hips but was not noticed above the hips. There was generalized hyperreflexia with positive Babinski signs, but the abdominal reflexes were absent. The extraocular movements were intact. No nystagmus was present and the speech was moderately slurred but much improved. The fundi were normal. His impression was "marked improvement since last examination. This could be called a remission stage."

The patient two months post partum showed definite improvement and had gained in strength. She had regained considerable use of her arms and legs. She was receiving constant physiotherapy, and was attending a walking class as well as occupational therapy classes. A pelvic examination showed the uterus to be normally involuted and the episiotomy well healed.

During her entire hospitalization supportive therapy was given. This consisted of adequate fluid intake, a high vitamin and high caloric diet with vitamin supplement, three whole blood transfusions totaling 1,500 c.c., and penicillin during the febrile courses. She was then fairly well until March 21, 1948, at which time she was transferred to the Valley Forge Army Hospital. Shortly after admission there was a moderately severe exacerbation of the disease, and physiotherapy, a course of histamine, and other forms of therapy were administered without any noticeable change in the course of the disease. Despite all efforts in her behalf, she followed a steady downhill course and, in accordance with her wishes, was returned to her home in Ireland on Feb. 21, 1949, after 16 months of hospitalization in this country.

CASE 3.—This 19-year-old white woman, gravida i, para 0, was first seen in this clinic on June 19, 1950, in the twenty-sixth week of pregnancy. Approximately one year prior to admission she had noted the gradual onset of numbness and tingling over both surfaces of the left foot. Presuming these symptoms to be unimportant she did not seek medical attention until one month later. At that time there was definite weakness of the left foot and leg. The paresthesia had extended upward to involve the entire left lower extremity. She was referred at that time to a neurologist who, after making the diagnosis of multiple sclerosis, treated her with histamine, 1 c.c. subcutaneously daily. The dosage was gradually reduced to three times weekly over a period of about four months. During this time there was an extension of the numbness over the posterior lower portion of the left trunk and weakness of the left leg associated with transient diminution of position sense in that extremity. There were no visual, speech, or other cranial nerve dysfunctions.

Severe frontal and vertical headaches developed, and the patient was sent to the Cleveland Clinic where the headaches were diagnosed as being due to the histamine. The histamine was omitted and treatment with Etamon begun and continued until the fifth month of pregnancy. Her course thereafter was one of steady improvement.

Physical examination in the prenatal clinic, from an obstetrical standpoint, was within normal limits. A normal intrauterine gestation of 26 weeks' duration was found. The vertex was presenting in a left occiput anterior position. The fetal heartbeat was 144 in the left lower quadrant. The pelvic measurements were within normal limits. Medically speaking, her only symptom was an altered, but not absent, ability to distinguish between hot and cold when applied to the left lower extremity.

The blood pressure was 124/76. The apical rate was 72. Hoffmann and Babinski signs were negative. The biceps, triceps, knee, and patellar reflexes were 3 plus on the right and 1 plus on the left. Ankle reflexes were active and equal. Cranial nerve function was intact.

The fundi were well outlined and essentially normal except for a suggestion of "chalkiness" at a depth of the right optic fundus. There was a diplopia on extreme upward and outward gaze to the right. There was no apparent loss of sensory response. Proprioceptive sense was intact. There was no apparent motor weakness or clonus.

She was followed through the remainder of her prenatal course and her health remained good. Laboratory reports were normal. She was Rh positive. The total weight gain during pregnancy was 27 pounds.

The patient was admitted in active labor near term on Sept. 18, 1950. After a normal rapid labor of six hours, she was delivered of a living female infant by low forceps, and with general anesthesia. A right mediolateral episiotomy was performed. The placenta was delivered intact and the episiotomy repaired in routine fashion. The postpartum course was normal. She was seen in the Medical Service on the fourth postpartum day and no evidence of recurrence was found and no further therapy advised. She was discharged with her baby on the fifth postpartum day. At the time of her postpartum check-up, six weeks later, no evidence of further recurrence of the disease could be demonstrated. Unfortunately, further follow-up of this patient was not possible.

Comment

The early literature on multiple sclerosis with concomitant pregnancy[1, 2, 3, 4] suggested that pregnancy produced an exacerbation in the disease and that interruption was indicated.

The opinion of clinicians in this country has been somewhat less definite,[5, 6] but when there are decided signs of progress in the symptoms termination of the pregnancy is favored. However, Tillman,[9] in an excellent review of the literature, pointed out the fact that pregnancy has no definite consistent untoward effect on the course of multiple sclerosis, since the disease process itself is noted for exacerbations and remissions. Thus, it was shown that the incidence of multiple sclerosis and the frequency of its recurrence were no greater in the multiparous woman than in the nulliparous or single. There is a noticeable lack of consideration given in the literature to that group of patients with multiple sclerosis who go through pregnancy without recurrence or exacerbation of the disease. These cases are all too frequently ignored because they lack interest and drama.

Tillman pointed out that patients in whom the disease was in a state of remission did well in pregnancy while those in whom the disease was unstable or progressive had exacerbations as a result of pregnancy. These facts were well demonstrated in Cases 2 and 3.

From all the present available evidence it would appear that multiple sclerosis does not increase the incidence of obstetrical complications. We encountered none in our series. The disease, at least in its early stages, apparently does not alter individual fertility. The puerperium in all of the cases has been uneventful. There appears to be no justifiable indication, either medical or obstetrical, for interruption of pregnancy. The therapeutic abortion included in this series was encountered at a time when the general feeling of the medical profession was to interrupt pregnancy if any definite progress in the symptoms was noted. However, Tillman suggests that in the rare case of bulbar involvement, therapeutic abortion may be a life-saving measure for the patient. There is no indication for termination of pregnancy and sacrifice of a child at a late stage in pregnancy unless bulbar involvement is present.

The second patient in this series was seen not only in a stage of exacerbation but almost *in extremis*—too ill to withstand any major procedure. A definite beginning of remission was noted prior to delivery and a normal rapid labor and puerperium followed. The infant showed no ill effects from the mother's disease.

The third case clearly demonstrates a remission of the disease occurring prior to and during an otherwise uneventful pregnancy and delivery. The infant was normal.

The third case also illustrates the change in the trend of medical thinking. There is considerable doubt that therapeutic abortion in any way alters the eventual outcome of the disease.

We do not believe that the outcome of any small series of patients should tend to formulate opinion, particularly in a condition as rare as multiple sclerosis. Since remissions and exacerbations are entirely unpredictable, such formulation becomes even more hazardous. Moreover, because of the gross unpredictability of the course of this disease, we believe that the few patients reported constitute grossly inadequate data on which to base dogmatic rules for handling.

Therefore, we feel that the effect of pregnancy on multiple sclerosis should not be considered a closed book and that further observation and individualization of the situation will result in optimal care for these patients.

Summary

Three cases of multiple sclerosis associated with pregnancy are reported. Two pregnancies were carried successfully to term and one was terminated in the first trimester without evidence of a change in the course of the disease.

The relationship of pregnancy to exacerbations in multiple sclerosis is still vague and requires further study. Each patient should be treated individually. Her age, parity, desire for children, and the stage and severity of the disease should be considered. Women in whom the disease is in remission will probably do well in pregnancy. If gestation takes place during an acute exacerbation, however, the prognosis may be somewhat less favorable.

The management of multiple sclerosis in pregnancy should be supportive and involve special consideration of the common complications such as hyperemesis, miscarriage, blood loss, and renal infection. The occurrence of these complications is said to aggravate the disease further and in some cases may precipitate acute exacerbations.

While vaginal delivery is desirable, cesarean section may, in some cases, be the most conservative. The method of delivery should depend solely upon the obstetrical indications.

At present there appears to be no clear-cut indication for termination of pregnancy when it is associated with multiple sclerosis.

Since there is a familial tendency in this disease, a prolonged study of the female infant would be of interest.

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SICKLE-CELL ANEMIA COMPLICATED BY PREGNANCY

A Review of the Literature and Six Case Reports

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A REVIEW of the literature from 1924 through December, 1951, reveals that a total of 77 cases of sickle-cell anemia complicated by gestation had been reported. With the addition of our six cases, the total is now 83. These 83 patients experienced a total of 176 reported gestations and had 100 successful pregnancies.

Sickle-cell anemia, a hereditary disease, is a chronic hemolytic anemia which occurs only in the Negro race. It is known by many names including sicklemia, drepanocytemia, meniscocytosis, and Herrick's syndrome.

Case Reports

CASE 1.—A 27-year-old Negro woman, para i, gravida ii, was first seen in March, 1939. The last menstrual period was Nov. 1, 1938. The estimated date of confinement was Aug. 8, 1939. Laboratory data were: hemoglobin 45 per cent; red blood count 2.8 million; white blood count 12,300; reticulocytes 6 per cent. An occasional nucleated red blood cell was seen. There was 35 per cent sickling of the erythrocytes in 18 hours. The serology was negative. The previous pregnancy resulted in a term stillbirth.

In May, 1939, the patient was admitted to the hospital complaining of chills, fever, and chest pain. The clinical impression was bronchopneumonia and pyelitis. Laboratory data were: hemoglobin 41 per cent; red blood count 2.12 million; white blood count 29,240; hematocrit 19; mean corpuscular volume 89.6; mean corpuscular hemoglobin concentration 30.1. There was marked anisocytosis, poikilocytosis, and 32 per cent sickling of the erythrocytes. Platelets were normal in number. Urine culture was positive for *Escherichia coli.* There was a marked elevation of temperature for five weeks while the patient responded slowly to whole blood transfusions and sulfanilamide. After discharge, she delivered at home a stillborn infant on June 27, 1939.

The patient was next seen on Aug. 8, 1940, approximately 16 weeks pregnant, complaining of chills and fever. The diagnosis was pyelitis. The patient was admitted to the hospital. Laboratory data were: hemoglobin 39 per cent; red blood count 2.17 million; white blood count 36,640; urine culture, positive for *E. coli.* Whole blood transfusions, sulfanilamide, calcium mandelate, and ammonium chloride were given for the anemia and pyelitis. She improved initially but on the ninth hospital day she became irrational, comatose, and died suddenly. Carbon dioxide combining power of the blood just prior to death was 14 volumes per cent.

Pertinent autopsy findings were: (1) a 4½ month intrauterine pregnancy; (2) bilateral old pulmonary tuberculosis; (3) hepatomegaly; (4) small fibrotic spleen; (5) chronic pyelonephritis. It was the pathologist's and our impression that the patient died in severe acidosis.

CASE 2.—A 24-year-old Negro woman, para i, gravida ii, was first seen in May, 1944. The last menstrual period was Jan. 15, 1944. The estimated date of confinement was Oct. 2, 1944. Laboratory data were: hemoglobin 63 per cent; red blood count 3.27 million; white

blood count 19,920; Rh positive. There was 80 per cent sickling. The patient was transfused with 500 c.c. of whole blood. On July 19, 1944, the hemoglobin was 42 per cent and 500 c.c. of whole blood was administered.

On Aug. 9, 1944, the patient was admitted to the hospital and delivered of a 7 month stillborn infant that weighed 828 grams.

The patient was next seen on Jan. 31, 1945. The last menstrual period was Nov. 13, 1945. The estimated date of confinement was Aug. 20, 1945. Laboratory data were: hemoglobin 59 per cent; red blood count 3.35 million. Severe pre-eclampsia developed and she was readmitted on May 30, 1945. The blood pressure was 200/122. Three plus pitting edema and 2 plus albuminuria were present. Laboratory data were: hemoglobin 59 per cent; red blood count 3.04 million; white blood count 14,120; reticulocytes, 2.5 per cent; platelets, 240,000. Marked anisocytosis and poikilocytosis were seen. The serology was negative. Under heavy sedation the blood pressure dropped. On June 8, 1945, a macerated stillborn infant was delivered. The patient had a very severe febrile course post partum but recovered.

CASE 3.—A 21-year-old Negro woman, para iv, gravida v, was first seen in February, 1945. At this time she was complaining of malaise and generalized aches and pains. The last menstrual period was Aug. 15, 1944. The estimated date of confinement was May 22, 1945. Laboratory data were: hemoglobin 53 per cent; red blood count 2.9 million; white blood count 20,090; Rh positive; reticulocytes 11 per cent; hematocrit 22, mean corpuscular volume 89.9, mean corpuscular hemoglobin 33.8. There were many nucleated red blood cells. Platelets were normal. There was marked anisocytosis and poikilocytosis. The serology was negative. After she received 500 c.c. of whole blood, the hemoglobin was 70 per cent. On April 27, 1945, she had a 3 plus albuminuria and microscopic hematuria. The clinical impression was renal thrombosis secondary to sickle-cell anemia. She was delivered at home of a 7 pound viable infant.

The patient was seen with her next pregnancy on Oct. 1, 1946. The last menstrual period was April 18, 1946. The estimated date of confinement was Jan. 26, 1947. Laboratory data were: hemoglobin 55 per cent; marked sickling.

The last visit was July 12, 1948. Her parity was vii. The last menstrual period was March 18, 1948. The estimated date of confinement was Dec. 25, 1948. Laboratory data were: hemoglobin 62 per cent; red blood count 3.4 million.

CASE 4.—An 18-year-old Negro woman, para 0, gravida i, was first seen in May, 1945. The last menstrual period was Nov. 7, 1944. The estimated date of confinement was Aug. 14, 1945. Laboratory data were: hemoglobin 62 per cent; red blood count 3.24 million. There was 58 per cent sickling. The serology was negative. The patient had a past history of rheumatic heart disease and chronic glomerulonephritis.

The patient was admitted to the hospital in premature labor on June 12, 1945. Laboratory data were: hemoglobin 47 per cent; red blood count 2.3 million; white blood count 13,840; Rh positive; hematocrit 21.8; mean corpuscular volume 94.8; mean corpuscular hemoglobin concentration 33; color index 1.1. There was 80 per cent sickling. Reticulocytes were 2.9 per cent. There were several nucleated red blood cells. Platelets were 200,000. There was marked anisocytosis and poikilocytosis. The blood pressure was 140/90 without other signs of toxemia. The patient ran a moderate febrile course. On June 14, 1945, she was delivered spontaneously of a stillborn infant weighing 1,805 grams. Ninety minutes post partum the patient became dyspneic and died suddenly. Autopsy was not permitted. The cause of death was not established. It was probably embolism.

CASE 5.—A 22-year-old Negro woman, para i, gravida ii, was first seen in July, 1945. The last menstrual period was Nov. 16, 1944. The estimated date of confinement was Aug. 23, 1945. Laboratory data were: hemoglobin 32 per cent; red blood count 1.04 million; white blood count 18,000; Rh negative; reticulocytes 23 per cent. Many nucleated red blood cells were seen. There was 98 per cent sickling. The serology was negative. A previous pregnancy terminated with a stillbirth at 7½ months. The patient was admitted and im-

mediately received 1,500 c.c. of whole blood. The following day a viable, 2,251 gram infant was delivered. In the early puerperium 1,500 c.c. of whole blood was given. Save for a mild febrile course the puerperium was uneventful. Examination of the peripheral blood of the infant did not reveal sickling of the erythrocytes.

CASE 6.—A 30-year-old Negro woman, para 0, was first seen in August, 1947. The last menstrual period was Feb. 23, 1947. The estimated date of confinement was Nov. 30, 1947. Laboratory data were: hemoglobin 60 per cent; red blood count 3.05 million. There was marked sickling of the erythrocytes. The serology was negative.

On Nov. 30, 1947, a viable 2,850 gram infant was delivered in the hospital. Laboratory data were: hemoglobin 53 per cent; red blood count 2.85 million; white blood count 20,000; Rh positive; reticulocytes 13.2 per cent; hematocrit 25; mean corpuscular volume 88; mean corpuscular hemoglobin 28; mean corpuscular hemoglobin concentration 32. Several nucleated red blood cells were seen. There was 80 per cent sickling. Platelets were 277,000. Examination of the peripheral blood of the infant did not reveal sickling of the erythrocytes. The patient had a mild febrile course.

The patient was readmitted on Nov. 18, 1948, at which time she was near term. Laboratory data were: hemoglobin 53 per cent; red blood count 2.6 million; white blood count 13,250; reticulocytes 11.7 per cent; hematocrit 22; mean corpuscular volume 85; mean corpuscular hemoglobin 30; mean corpuscular hemoglobin concentration 36. Many nucleated red blood cells were seen. There was marked anisocytosis and poikilocytosis. She was given 500 c.c. of whole blood. On Nov. 26, 1948, a viable 2,700 gram infant was delivered. The postpartum course was afebrile.

Comment

The diagnosis is contingent upon the demonstration of the bizarre sickle-shaped erythrocytes in the peripheral blood. Because this change is not always immediate, preparations should be examined for 24 hours. This sickling associated with a normochromic, normocytic anemia is diagnostic. The hemoglobin is usually 55 per cent or lower and the red blood count usually 3 million or lower. Other frequent laboratory findings are reticulocytosis, leukocytosis, thrombocytopenia, and immature erythrocytes in the peripheral blood.

The symptoms and signs of sickle-cell anemia are varied and not specific. Anemia is always found. Some common manifestations are weakness, jaundice, cardiac murmurs, chronic leg ulcers, abdominal pains, joint pains, and headaches. The nebulous symptoms are the result of the physical properties of the abnormal erythrocytes. Their bizarre shape makes for the formation of thrombi with infarction and pain. Their fragility produces hemolysis, and anemia. The wide range of symptoms results in occasional mistaken diagnoses. The most frequent are rheumatic heart disease, appendicitis, cholecystitis, and ruptured peptic ulcer.

Sickle-cell anemia must not be confused with sicklemia. The latter denotes a condition in which the erythrocytes exhibit the sickling phenomenon, but it is not associated with anemia. It is of no consequence and the patients show no ill effects. It is compatible with long life whereas sickle-cell anemia results in the relatively early demise of the patient.

Killingsworth and Wallace[11] found sicklemia in 7 per cent (684) of 9,658 Negro patients whereas but one in 15 of these had sickle-cell anemia.

Table I gives the result of the 157 previously reported gestations as well as our series of 19 patients, only 10 of whom received any prenatal care here.

The fetal salvage was 59.2 per cent in the former and 36.8 per cent in the latter. Of those 10 pregnancies in which prenatal care was given at Duke Hospital the fetal salvage was 50 per cent. We now believe that the more liberal use of whole blood transfusions will improve fetal salvage.

TABLE I. FETAL SALVAGE IN 176 PREGNANCIES IN 83 PATIENTS WITH SICKLE-CELL ANEMIA

	PREGNANCIES REPORTED IN LITERATURE	PREGNANCIES REPORTED AT DUKE HOSPITAL	TOTAL	PERCENTAGE
Total gestations	157*	19†	176	100
Abortions	22 (14%)	4 (21%)	26	14.7
Stillbirths	12 (7.6%)	6 (31.5%)	18	10.2
Live births	102 (64.9%)	7 (36.8%)	109	61.9
Neonatal deaths	9 (5.7%)	0	9	5.1
Died undelivered	8 (5.09%)	1 (5.2%)	9	5.1

*Four pregnancies were terminated by laparotomy and 2 unknown.
†One unknown.

Patients with sickle-cell anemia complicated by pregnancy are poor obstetrical risks, not only for reason of the anemia per se but also because of the complications which arise secondary to the anemia (Table II). These patients are most susceptible to infections. In Beacham's[3] report of 37 pregnancies associated with sickle-cell anemia, 28 had pre- or postpartum complications. Of the 53 patients in the literature, exclusive of Beacham's, there were 24 patients who had complications reported. Only 3 of the 10 pregnancies followed at Duke Hospital were without complications.

TABLE II. REPORTED COMPLICATIONS OF PREGNANCY AND THE PUERPERIUM IN 176 PREGNANCIES IN 83 PATIENTS WITH SICKLE-CELL ANEMIA

	PATIENTS REPORTED IN LITERATURE	PATIENTS AT DUKE HOSPITAL
Urinary tract infections	23	2
Puerperal morbidity	17	4
Toxemia of pregnancy	21	2
Renal thrombosis	0	1
Pneumonia	13	1
Tuberculosis	2	1
Upper respiratory infection	8	
Pulmonary infarction	4	
Cerebral thrombosis	4	
Meningitis	1	
Rheumatic heart disease	4	
Bacterial endocarditis	1	
Cardiac failure	2	
Thrombophlebitis	5	
Jaundice and fever	4	

The most common complication is infection of the urinary tract. Toxemia of pregnancy, puerperal morbidity, and respiratory infections follow in that order.

Of the 83 patients only 7 were over 30 years of age. The youngest patient in the literature was 16 years old and the oldest was 35. The youngest patient in the Duke Hospital series was 18 and the oldest was 31 years old. The fact that these patients usually die before the fourth decade of life explains the small number of patients seen over the age of 30 years.

The infant has been found to have sicklemia in 19 of 28 infants studied in Beacham's series, and in 15 of 28 infants in the remaining literature. Only two of our infants were studied and neither had sicklemia. There has been no known report to date of sickle-cell anemia occurring in any of the above children.

There were two maternal deaths at Duke Hospital. One patient (Case 1) died ante partum at 4½ months' gestation. The cause of her death was severe acidosis associated with ammonium chloride and calcium mandelate therapy. The second patient (Case 3) died 90 minutes post partum. The cause of death was thought to be an embolic phenomenon. The maternal death rate was 33.3 per cent.

There were 17 maternal deaths in the 77 patients reported in the literature. Seven of these patients died undelivered. Ten patients died postpartum. The maternal mortality rate for these patients is 22.1 per cent. For the total 83 patients the maternal death rate is 22.8 per cent.

Summary

This report covers 83 patients with sickle-cell anemia who had 176 reported pregnancies. In the literature we found 77 patients with 157 pregnancies. We have added 6 patients with 19 pregnancies. In 10 of these latter pregnancies some prenatal care was given at Duke Hospital.

Of the pregnancies reported to date only 56.8 per cent of the fetuses survived.

In 176 pregnancies the complications reported included 25 urinary tract infections, 23 cases of toxemia of pregnancy, 21 morbid puerperiums, 14 cases of pneumonia, 8 upper respiratory infections, 9 thromboses of the vascular system, as well as 14 other types of infection.

Maternal mortality was 22.8 per cent in the 83 patients.

Conclusions

1. All Negro obstetrical patients who are severely anemic should be investigated for sickle-cell anemia.
2. The prognosis for the fetus is very poor.
3. Severe infections are common and the incidence of toxemia is considerably increased.
4. The maternal risk is grave.

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PREGNANCY FOLLOWING BILATERAL DERMOID CYSTECTOMY

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CONSERVATISM is generally conceded to be a wise policy when pelvic surgery becomes necessary in the woman of childbearing age, particularly in her younger years. Most physicians who hold such a philosophy also practice it. Possibly there is room for improvement by all who do abdominal and pelvic surgery. The traditional management of dermoid cysts has usually been rather radical, but what has been accepted for years as more or less standard treatment may merit re-evaluation. The following two cases are reported as evidence that one may be conservative in the treatment of this particular lesion when it is encountered during a woman's reproductive years, and regardless of whether or not it is associated with pregnancy at the time of discovery.

CASE 1.—(Swedish Hospital No. 43-9090.) Mrs. F. D., aged 25 years, married one year, was first seen in September, 1942, in the fourth month of her first pregnancy. Previous history was not pertinent. Menses started at the age of 13, had been regular at thirty-day intervals with a duration of five days. A diagnosis of early pregnancy, complicated by bilateral dermoid cysts, the latter confirmed by x-ray, had been made by the referring physician. Physical examination revealed a young woman of medium build, with normal general findings. Pelvic examination confirmed the presence of a uterus enlarged to the size of a four months' gestation, and bilateral, freely movable masses, each approximately 7 to 8 cm. in diameter. The diagnosis and management were discussed with the patient in detail. Mutual agreement and approval were given to a policy of conservative management. She pursued a normal prenatal course, and at term in March, 1943, delivered a normal 7½ pound male child, after a short, uneventful labor. She had an average amount of breast engorgement but did not nurse her baby.

Several months post partum, the patient began to experience annoying episodes of lower abdominal pain. Examination revealed a slight increase in the size of the cysts. Laparotomy was advised. Since she was extremely anxious to have further children, I assured her that conservatism, if at all possible, would be employed in the removal of these cysts. On Sept. 30, 1943, curettage and laparotomy were performed. The right ovary was found to be converted into a cystic mass characteristically dermoid in appearance and measuring 8 cm. in diameter. At the base of this mass could be seen a recent corpus hemorrhagicum. The left ovary was composed of a similar but slightly smaller mass, with no normal-appearing ovarian tissue present, and had to be completely removed. The cyst on the right ovary was then resected, preserving a small amount of ovarian tissue at the hilus aggregating considerably less than the equivalent of a normal-sized ovary. The post-operative course was nonmorbid and uneventful. The pathologist's examination revealed the usual contents in cysts of this type.

The patient presented herself again in April, 1945, because of symptoms of early pregnancy, and examination revealed findings consistent with an early intrauterine gestation. Blood studies revealed the additional fact that the patient was Rh negative and her husband positive. The pregnancy progressed normally. In November, 1945, I delivered her again at term, the baby being a normal 8 pound, 6½ ounce female child. She had the usual amount of breast engorgement, but did not nurse.

In January, 1947, the patient again presented herself for pregnancy care, and again proceeded uneventfully to term. In August, 1947, I delivered her of a normal male child, weight 8 pounds, 6 ounces. She nursed her baby this time for one month.

The patient was seen next in September, 1949, because of a mild aberration in her menstrual cycle, which shortly proved to be another pregnancy. She made inquiry as to what could be done after delivery of this baby to stop the reproductive process which was proving to be far more fruitful than anticipated. During the eighth week of this pregnancy, she reported slight bleeding, unaccompanied by pain or cramps. She was placed on diethylstilbestrol and oral progesterone, 25 mg. of each daily. The bleeding continued in an intermittent fashion for about two weeks. The progesterone was continued through the fifteenth week of the pregnancy, and the stilbestrol was increased 5 mg. weekly, until she was taking 75 mg. daily, and this was continued through the thirty-fifth week of the pregnancy. Anti-Rh titer was secured in the thirty-fourth week, and reported to be one to eight. A repeat titer was ordered several weeks later, but the patient did not have it done. In June, 1950, at term, she was delivered of an apparently normal male child, who weighed 7 pounds, 4 ounces. He showed no evidence of erythroblastotic disease. There was an average amount of breast reaction, and she started to nurse her baby. At the request and consent of the patient and her husband, and with my approval, postpartum sterilization, utilizing the Pomeroy technique and absorbable sutures, was performed on the fourth postpartum day. At the time of operation, the ovary could not be well visualized because of adhesions surrounding it, but it was palpated as a mass about the size of an almond. Having had the opportunity to see and feel this small structure for a second time, I have remained astonished to consider how well it had served its biologic role. The patient has been seen at periodic intervals since. Menses have been essentially normal; there have been no symptoms of waning ovarian function, and pelvic examination is negative.

CASE 2.—(Swedish Hospital No. 45-3472.) Mrs. S. W., aged 27 years, married four years, first presented herself for consultation in February, 1945. Her complaints were right lower abdominal and suprapubic pain, dating back several years, with bladder frequency and urgency, severe dysmenorrhea, and profuse menstrual flow. Previous history revealed no pertinent illnesses. Menses had their onset at age 13, were regular at twenty-eight day intervals, with a duration of six days. There had been one suspected but unproved pregnancy shortly after marriage. Physical examination revealed a young woman of slender build, appearing well. Abdominally, there was a mass palpable just above the pubis. Pelvic examination revealed what was thought to be a moderately enlarged uterus, firm, irregular, and freely movable. The regions of the adnexa were clear. A diagnosis of pelvic tumor, probably fibromyoma, but possibly ovarian in origin, was made. The findings were explained to the patient, and surgery, with conservation of ovarian and childbearing function, if at all possible, was advised. The patient, desirous of having children, was extremely concerned over the possibility that castration might be unavoidable.

On April 17, 1945, dilatation and curettage and laparotomy were performed. The uterus was found to be normal. The right ovary was converted into a 9 cm. cystic tumor mass which grossly resembled a dermoid. The left ovary was converted into a similar but slightly smaller mass, which had come to lie more or less in the midline, with the uterus lying between these two cystic structures. At the base of the left ovary, in the hilus region, could be seen a recent corpus hemorrhagicum and corpus luteum. The right ovarian mass was completely excised, since there was no discernible normal-appearing ovarian tissue. The left ovarian cyst was resected, leaving a mass of tissue about 3 cm. long, 2 cm. wide, and 1 cm. thick, which tissue contained the corpus hemorrhagicum and corpus luteum. The diagnosis of dermoid cyst of the right and left ovaries was confirmed by the pathologist, and microscopic examination showed no evidence of malignancy. The postoperative course was nonmorbid and uneventful. She experienced no further pain nor menorrhagia, and the dysmenorrhea was almost totally relieved.

The patient presented herself again for consultation in November, 1946, approximately eighteen months after her surgery, having felt well during the interim, and suspecting now

that she was pregnant. Examination confirmed this suspicion. The pregnancy progressed normally, and in July, 1947, she was delivered at term of an apparently normal female child, who weighed 9 pounds, 8 ounces. She did not nurse. She has been seen at periodic intervals since. Her menses have been essentially normal; there has been no evidence of waning ovarian function, and pelvic examination is negative.

Comment

The histogenetic and general clinical aspects of dermoid cysts are sufficiently well known to all to preclude the need for any extensive review. For excellent discussions of both the pathological and clinical features of these tumors, the reader is referred to the writings of Geist,[1] Novak,[2] Faulkner and Douglass,[3] Curtis,[4] and Dockerty.[5]

In the literature, references to the management of bilateral dermoid cysts complicating pregnancy are not abundant. Notes[6] reported finding only three such cases up until 1938, and added one of his own. Andrews and co-workers submitted a study of forty-two additional cases and added one of their own. Southward[8] reported one case in 1940. King[9] added another in the same year. Doyle,[10] Goodwin,[11] Ellis,[12] and Nuccio[13] each added a single case in 1942. Bowles,[14] also in 1942, reported an additional five cases. In 1947, Berlind[15] added another case, and Falk[16] reported two more in the same year. Reitman[17] added one in 1948, and Heffernon[18] reported another case in 1950. The most recent report seen is that of Barber,[19] in 1951, who has gleaned from the literature five other cases, some of them in the foreign literature, and has added one case of his own.

The cases of bilateral dermoid cysts complicating pregnancy, including the one reported here, now number seventy. Based upon these earlier reports, the consensus seems to be that when bilateral dermoid cysts are encountered in early pregnancy, it is better to postpone laparotomy and removal of the dermoids until after the corpus luteum is no longer necessary, with the fourth month being generally agreed as the optimum time for operation. A further conclusion, as a result of the study of the management of these reported cases, is that, if the diagnosis is made only shortly before viability, watchful waiting is indicated until the fetus is viable, at which time cesarean section and operation on the cysts are carried out. It seems to me that these conclusions are not entirely valid, since they are based on the premises that all dermoid cysts must inevitably undergo torsion, will obstruct labor, will be malignant, or would behave in some way that would make their conservative management inevitably hazardous.

In these earlier reported cases, there are also many instances of spontaneous late abortion and early premature labor which occurred when surgery for dermoids was done after the fourth month, undoubtedly due to such contributing factors as manipulation, trauma, blood loss, and anesthesia. The fact that the surgery is postponed until the fourth month or later is no guarantee that the pregnancy will continue successfully. Hence, if surgery during pregnancy can be safely postponed, fetal loss from these incidental factors could be eliminated.

References in the literature to the *conservative* management of bilateral dermoid cysts discovered in early pregnancy, or at any other time, are extremely meager. Only eight such references could be found, and they were in the cases reported by Southward,[8] Nuccio,[13] Heffernon,[18] Bowles,[14] Falk,[16] and Barber.[19] The latter, in his recent report, states that out of the sixty-six cases which he reviewed, only ten were treated conservatively with preservation of ovarian tissue. Eight of these are, no doubt, duplicates. In Southward's[8] case, the patient was operated upon for bilateral dermoids during the fourth month of pregnancy, with conservation of a bit of ovarian tissue, the patient going on successfully to term and having a second child two years later. Levi,[20] in 1948, reported two cases of bilateral dermoid cysts in which conservative surgery was performed, dime-sized portions of tissue being preserved. One patient, who married later, was subsequently delivered of three normal children. There probably are other cases in which conservative surgery has been practiced in situations of this kind, but there is a paucity of reports in the literature.

One is compelled to ask, then, what is the reason for the radical approach when dealing with dermoid cysts, both during pregnancy and in the nonpregnant woman? Apparently, the main reason is the fear that malignancy, based on the premise that a recurrence, or a metastatic spread of malignant cells in and from any ovary which has been the site of a conservatively resected dermoid cyst, might occur. Actually, this fear of malignancy is probably not justified. The incidence of malignancy in dermoid cysts has generally been assigned as from 1 to 3 per cent. Novak[2] states, "While the dermoid is a perfectly benign tumor, secondary malignant degeneration may occasionally occur in the form of either sarcoma or carcinoma." Geist[1] points out how both benign and malignant tumors may arise from dermoid structures and form part of the neoplasm. He reports an incidence of 1 per cent of secondary malignant tumors in dermoid cysts. The majority of these secondary tumors are squamous-cell carcinomas. Martzloff,[21] in reporting cases at Johns Hopkins Hospital, states, "Out of a total of some two hundred patients who have had dermoid cysts in one or both ovaries (confirmed by examinations of microsections), we have had only one other case (two altogether) of carcinoma developing in an ovarian dermoid cyst." Marshall,[22] in reporting four hundred fifteen cases from the Mayo Clinic, reported an incidence of 1.9 per cent malignancy in dermoids. Nowhere in the literature on dermoid cysts could I find a report of the development of a malignant process manifesting itself as a recurrence, metastasis, or direct extension of the original neoplasm, subsequent to the performance of conservative surgery wherein some normal-appearing ovarian tissue had been preserved.

While actual case reports are meager, there are a considerable number of pleas in the literature (Miller,[23] Geist,[1] Levi,[20] Bell,[24] Meigs,[25] Dockerty,[5] Helwig,[26] and Brewer[27]) of the last three decades, particularly lately, stressing the wisdom, value, and minimal risk involved in the resection of dermoid cysts, leaving some ovarian tissue to protect against the surgical menopause, and to preserve the childbearing function in the young woman.

Summary and Conclusions

Two cases of bilateral dermoid cysts occurring in young women in the childbearing years are reported. In the first patient, the tumors were discovered in early pregnancy, and surgery was postponed until after an uneventful labor and successful delivery. Conservative surgery was practiced, with preservation of a small bit of one ovary. The patient has had three subsequent pregnancies and is enjoying normal health nine and one-half years later. In the second patient, surgery for bilateral dermoids was performed prior to pregnancy, and with the same conservative policy displayed. She has had one subsequent pregnancy, and is enjoying good health eight years later. The management of these two cases suggests that when bilateral dermoid tumors are discovered during early pregnancy, early operation is not necessary, cesarean section is not inevitable, nor is radical extirpation of the ovaries imperative when surgery finally is done. Furthermore, when the cysts are discovered and operated upon prior to pregnancy, as in the second instance, conservation of normal ovarian tissue can be accomplished, and is desirable in the interests of future childbearing and avoidance of the creation of a surgical menopause in a young individual.

A study of the literature reveals that a radical approach has been more or less traditional in this problem, but highly valid and authentic reasons have not been documented which would serve to indict a more conservative policy. Apparently, the outstanding reason for the radical approach has been a fear of malignancy, which fear is hardly substantiated by the actual incidence of malignant changes in dermoid cysts, since the figures from many clinics and by many authorities suggest that the percentage of malignant dermoids is very small, and that these malignant changes are generally confined to secondary malignant degeneration of some of the intracystic contents.

While no startling conclusions can be drawn from the two cases reported, it is hoped that others will be stimulated to follow a conservative policy in situations of this kind. Only when we have an adequate body of background experience and information will we be able to advocate a strict policy as to what should be done in the management of these patients. Prevention of the surgical menopause, and preservation of the childbearing function in the young woman are admittedly commendable goals. The evidence would seem to indicate that this can be accomplished in patients with bilateral dermoid cysts, at little or no risk. An attitude of enlightened skepticism toward the traditional radical management of these lesions by the physicians who are responsible for making these important decisions would, I am sure, result in a much more conservative policy, which, in turn, would lead to improved and sustained good health, preserved reproductive capacity, and immeasurable happiness in the lives of these young women patients.

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CARCINOMA IN SITU OF THE CERVIX: RECURRENCE IN THE VAGINAL VAULT

Report of a Case

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RECENT observations by Younge, Hertig, and Armstrong[1] indicate that carcinoma in situ of the cervix uteri is a biologic entity and partakes of many if not all of the characteristics of malignant neoplasms in general. Even more recently, Galvin, Jones, and Te Linde[2] have reported on the development of invasive carcinoma of the cervix following a diagnosis confirmed by biopsy of carcinoma in situ; they were able to locate 30 such cases adequately documented in the literature and added 10 cases from their own experience. At about the same time, Petersen[3] reported on a group of 104 cases in which five to twelve years had elapsed since the initial biopsy. He found that invasive carcinoma had developed in 14 of the 54 patients whose initial biopsies showed either "nuclear abnormalities" in the surface epithelium or extension of "abnormal" epithelium into endocervical glands, an incidence of 26 per cent.

Comparatively little attention has been focused upon another property of neoplasms in general which carcinoma in situ may exhibit, namely, recurrence at the site of excision. The following case is presented to illustrate this feature as well as to point out certain considerations which must underlie treatment of the lesion.

Case Report

ARMED FORCES INSTITUTE OF PATHOLOGY ACCESSION 282001.—A 35-year-old white housewife, gravida iii, para ii, abortion 1, was first seen at Fitzsimmons Army Hospital on Sept. 1, 1949, complaining of intermenstrual and postcoital spotting of two months' duration. Physical examination at that time was noncontributory, and inspection of the cervix revealed only a parous cervix. A biopsy taken at random from the anterior lip of the cervix showed nuclear abnormalities and disturbed stratification; the fragment of tissue removed was so small that another biopsy was advised.

The second biopsy was performed on Oct. 24, 1949, and a diagnosis of squamous carcinoma in situ was made. Several fairly long, well-oriented strips of cervical tissue were excised. The surface epithelium was in many areas converted into neoplastic epithelium, characterized by pronounced loss of polarity, disturbance of stratification, cellular pleomorphism including cells with large, bizarre nuclei, and increased mitotic activity. This neoplastic squamous epithelium extended into the necks and bodies of the endocervical glands, lifting off the columnar glandular epithelium in the manner which typifies this lesion. Not all the squamous epithelium was converted into neoplastic epithelium. In

some foci there was active hyperplasia of basal and parabasal cells with surface maturation and stratification; in these areas mitotic activity was low and confined to the basal and adjacent layers, and there were no "tumor giant cells." In addition, patches of normal stratified squamous epithelium were present, and all stages of transition from normal to hyperplastic to frankly neoplastic epithelium could be identified. Of some interest was the topographic arrangement of these different stages in the process, particularly in relation to the glandular epithelium of the endocervix. The areas characteristic of carcinoma in situ were separated from each other by normal and/or hyperplastic squamous epithelium, giving the impression that the tumor was of multicentric origin. On the basis of this biopsy, total hysterectomy and left salpingo-oophorectomy were performed on Nov. 2, 1949.

On examination of the hysterectomy specimen, the uterus was found to weigh 65 grams, the body measuring 5 by 4 by 3.5 cm., and the cervix to measure 3.5 cm. in length by 3 cm. in diameter at the external os. A cuff of vaginal mucosa measuring 1.2 cm. anteriorly and laterally and 0.8 cm. posteriorly was described. The external os was round, 1.2 cm. in diameter, and surrounded by a zone of superficial erosion, 0.5 cm. in width. The endocervical canal was 2.8 cm. in length, and contained a few cystic polypoid structures arising from relatively thick bases with their apices pointing toward the external os; the largest of these measured 1.2 cm. in length. The only gross lesions detected on examination of the corpus uteri, the left tube and ovary, were a few small cystic structures in the ovary. The specimen was fixed in its entirety after it was opened, and multiple blocks were taken through the cervix and through the vaginal cuff. Microscopically, a few residual foci of squamous carcinoma were found in the cervix. These were confined to the surface epithelium and a few endocervical glands; no invasion of the cervical stroma was seen. Examination of the vaginal cuff in several sections showed it to be free from tumor or from any epithelial change suggesting neoplastic growth. Chronic cervicitis with Nabothian cysts was also present. The left ovary contained several follicle cysts and one corpus luteum cyst.

On Jan. 30, 1952, 27 months after the hysterectomy, the patient was examined at the Tokyo Army Hospital. No clinical evidence of recurrence was noted. However, a small amount of tissue was taken from an area that was denuded of epithelium supposedly because of trauma at the time of examination. Microscopic examination of this tissue (20391) at the 406th Medical General Laboratory showed that it was covered with squamous epithelium, a portion of which, while not abnormal, contrasted sharply with another area intrepreted as chronic vaginitis with epithelial unrest. A sharp line of demarcation between the two types of epithelium ran perpendicular to the epithelial surface. This material was reviewed at the Armed Forces Institute of Pathology in April, 1952, and despite the small size of the specimen there appeared to be justification for the histologic diagnosis of recurrent carcinoma in the vaginal vault. However, it was recommended that another biopsy be performed before transferring the patient to the United States for definitive therapy. This biopsy was performed at the Tokyo Army Hospital on June 10, 1952, and reported as squamous carcinoma in situ, vaginal epithelium, by the 406th Medical General Laboratory.

The patient was admitted to the Walter Reed Army Hospital late in August, 1952. Biopsies of the vaginal vault on August 26 and September 5 were interpreted as squamous carcinoma in situ in the vaginal epithelium. Because of artifacts in the sections, focal superficial invasion of the underlying stroma could not be ruled out. The tissue was taken from an area in the vaginal vault that was described as reddened and discolored, but whether this was because of the previous biopsies or because of the nature of the lesion could not be determined. On Sept. 12, 1952, almost three years after hysterectomy, the vaginal canal was excised and a plastic reconstruction performed.

The operative specimen measured 7 cm. in circumference and 4.5 cm. in length. The central portion, corresponding to the apex of the vaginal vault, contained an irregular area of brownish discoloration; the epithelium covering this area was thicker and less translucent than that in the peripheral portions of the specimen which corresponded to the

Fig. 1.

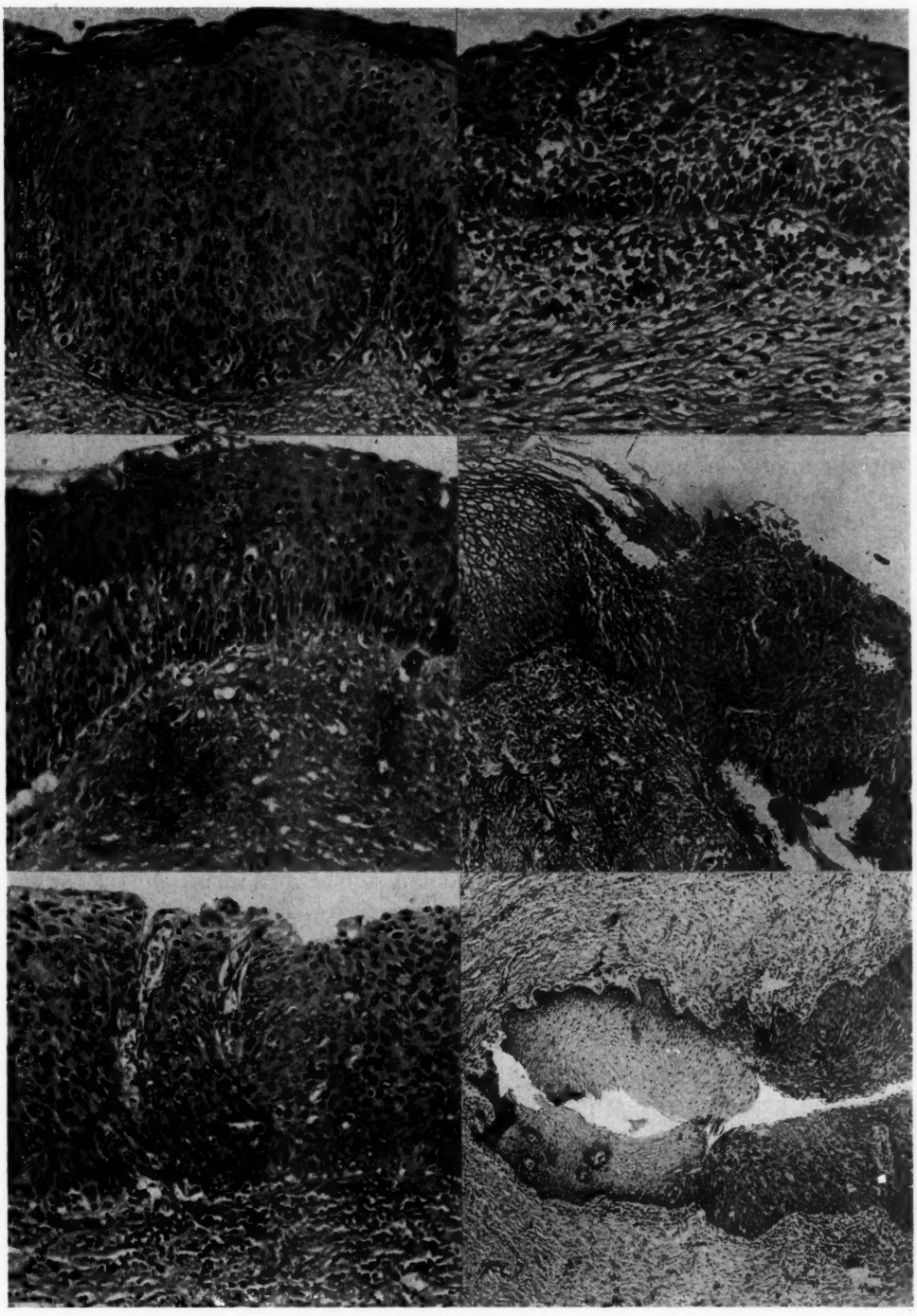

Fig. 2.

Fig. 3.

Fig. 4.

Fig. 5.

Fig. 6.

Fig. 1.—Second biopsy, cervix. Thickening of squamous epithelium and scalloping of rete pegs. Loss of organization and polarity, parakeratosis, increased mitosis. (×125.)

Fig. 2.—Same fragment. Thinning of epithelium, bizarre cells, intercellular edema. (×125.)

Fig. 3.—Same fragment. Shows merely basal and parabasal cell hyperplasia and mitotic activity. Stratification better preserved than in Fig. 1. (×125.)

Fig. 4.—Biopsy (vaginal vault) 27 months after hysterectomy. Perpendicular line of demarcation between normal glycogenated squamous epithelium and area of "epithelial unrest" interpreted as carcinoma in situ. (×75.)

Fig. 5.—Vaginectomy. Recurrent carcinoma in situ. Note vascularization of the neoplastic epithelium. (×125.)

Fig. 6.—Vaginectomy. Recurrent carcinoma in situ showing "spared area" between rugae of vaginal mucosa. Section is taken parallel to long axis of vagina. (×50.)

lower portion of the vagina. Microscopic examination revealed the squamous epithelium of the apex of the vagina to have undergone complete transformation into squamous carcinoma which was still in situ in all sections. This lesion was morphologically identical with that seen in the biopsies; in addition, there were areas in which the neoplastic epithelium was perforated by small blood vessels; the tumor cells tended to form whorls about these vessels in a pattern suggesting a flattened papillomatous type of growth. An occasional capillary perforated the epithelium almost to the free surface. Sections taken from the peripheral portion of the specimen, i.e., the lower part of the vagina, showed normal stratified squamous epithelium. The final anatomic diagnosis was squamous carcinoma in situ, vagina, recurrent from cervix uteri.

Comment

The important clinical feature in this case is the development of recurrent squamous carcinoma in the vaginal vault 27 months following hysterectomy for carcinoma in situ of the cervix. The hysterectomy specimen was described as having a cuff of vaginal mucosa measuring 1.2 cm. anteriorly and laterally and 0.8 cm. posteriorly. When allowance is made for the retraction of the epithelial surface on removal, this would appear to be a reasonable size for the vaginal cuff. There are two possible explanations for this recurrence. First, it is possible that the line of excision cut across neoplastic epithelium which was still in situ, and residual irreversibility neoplastic cells were left behind; however, examination of multiple sections of the vaginal cuff at the line of excision failed to reveal any epithelial changes suggestive of neoplasia. This serves to call attention to the necessity for meticulous pathologic examination of such lines of excision. The alternative hypothesis, admittedly speculative, does not permit of empirical validation. This hypothesis hinges on the observation that the squamous epithelium of the portio vaginalis of the cervix and the upper third of the vagina are both derived from the same source, namely, Müllerian epithelium. If the notion of a persisting, circulating, humoral carcinogenic stimulus is invoked, it is not difficult to apply its presumed action upon the remaining portion of the upper third of the vaginal mucosa as an end organ. If we apply the maxim that the surgical treatment of tumors must be based upon the pathology of the tumors, we must subsume under the broad term pathology both the mechanics of morbid anatomy and dynamics of pathogenesis.

The problem of selecting the appropriate treatment for a given case of carcinoma in situ of the cervix once a histopathologic diagnosis of the lesion has been unequivocally established is one filled with difficulties. The available literature on the subject is confused by many variable factors. Notable among these are the cases of carcinoma in situ which were "cured by biopsy," i.e., in which a second biopsy or hysterectomy failed to reveal the lesion. While in theory one may conjecture that a small carcinoma located at the squamocolumnar juncture might be completely removed by a single biopsy, the alarmingly high incidence of such cases makes one question the validity of the initial diagnosis. In still another group of cases there seems to have been no recurrence following treatment by cauterization, conization, or cervical amputation. Limited procedures of this type need not be contraindicated,

particularly in patients who desire to preserve reproductive function, but Pund and associates[4] have pointed out that these procedures may not be adequate because of nests of neoplastic cells lying deep in the endocervical glands or high in the endocervical canal. Most observers are of the opinion that some form of abdominal hysterectomy is the treatment to be used at the present time. Varying opinions regarding the advisability of removing the uterine adnexa and of performing more or less extensive pelvic lymph node dissection can be found in a cursory survey of the literature. The survey on methods of treatment of this lesion conducted by Hoge[5] shows the wide range of opinion regarding the most advantageous surgical treatment and even indicates that a substantial minority (18 per cent) prefers some form of radiation therapy. However, at least two large Scandinavian clinics pursue a policy of watchful waiting.[3]

Comparatively less attention has been directed to the upper third of the vagina, the only other mature squamous epithelium that is embryogenetically related to the cervical epithelium rather than to adnexal structures and pelvic lymph nodes. It is suggested that this area also be evaluated in the surgical treatment of carcinoma in situ. Possibly preoperative use of the test described by Schiller,[6] with careful inspection of the vaginal mucosa, might be helpful in delimiting the area to be excised. This is further indication of the continuing need for adequate biopsies and accurate interpretation as well as sound clinical judgment in the treatment of cancer.

Parenthetically, close microscopic inspection of this tumor, particularly as viewed in the second biopsy (S-2679-49), offers some support for the notion that carcinoma may originate in an epithelium as a "field response" rather than from a single cell or small group of cells which undergo malignant transformation and grow autonomously outward. This impression is gained from the presence of multiple discontinuous areas of carcinoma in situ separated by intercalated areas of normal and/or hyperplastic epithelium. The subsequent behavior of the neoplasm in the vaginal vault does nothing to alter the impression that in this patient the squamous epithelium of Müllerian origin in the cervix and vagina served as an end organ for some carcinogenic stimulus. However, this remains a hypothesis rather than an established fact. Evidence for and against the "field theory" of carcinogenesis, particularly in regard to carcinoma in situ of the cervix, is ably summarized by Stoddard.[7] The problem of multicentric origin of carcinoma in situ might well be approached by a careful three-dimensional study of excised cervices.

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Department of Case Reports New Instruments, Etc.

RECTAL HEMORRHAGE IN THE PUERPERIUM

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RECTAL hemorrhage in the puerperium is apparently a rare obstetrical complication. I could find no mention of this occurrence in any of the standard American or British obstetrical textbooks, nor reference to it in a perusal of the recorded literature for the past twenty years. A lesion that can cause serious late postpartum hemorrhage would seem to warrant wider recognition. The general subject of late postpartum hemorrhage has been discussed elsewhere[1] and will not be summarized at this time.

Case Report

A 30-year-old white primigravida experienced a normal pregnancy and began labor spontaneously at term. Delivery of a viable male weighing 7 pounds, 1 ounce (3,203 grams), was accomplished under continuous caudal anesthesia by low midforceps and right mediolateral episiotomy. The third stage was uneventful and the blood loss was 150 c.c. The early puerperium was complicated by urinary retention (relieved by intermittent catheterization) and superficial infection of the episiotomy which had healed by the eighth postpartum day when the patient was dismissed in satisfactory condition.

Upon her arrival home, which was one hour after dismissal from the hospital, the patient experienced a sudden profuse hemorrhage which she, a graduate nurse, thought was from the vaginal tract. When readmitted to the hospital half an hour later, the patient was in shock with blood pressure 70/20. There was fresh and clotted blood over the vulva and perineum. A transfusion of 500 c.c. of whole citrated blood was given and the patient was taken to the operating room, where dilatation and curettage were carried out under Pentothal Sodium anesthesia. Nothing was obtained but a few shreds of decidua. Because of the persistent state of shock a second transfusion of whole blood was given immediately after curettage.

The patient's condition remained satisfactory for thirty hours, when she had another profuse hemorrhage which was observed to come from the anus, not the vaginal tract. The patient remarked that just before the hemorrhage she had had the desire to defecate. After an estimated blood loss of 400 c.c. which occurred within twenty minutes, she again went into shock, the bleeding subsided, and a third transfusion of 500 c.c. of whole blood was administered. Digital examination of the rectum disclosed no abnormalities, nor did it provoke fresh bleeding.

Early the following morning (the tenth postpartum day) the patient had her third episode of severe rectal bleeding, which also was preceded by the desire to defecate. Shortly thereafter she was returned to the operating room where proctoscopic examination was carried out. The significant finding was the presence of an adherent blood clot on the anterior rectal wall about 10 cm. proximal to the anal orifice. Inasmuch as the clot appeared firmly adherent to an underlying ulcerated point about 0.5 by 0.5 cm. diameter,

it was not disturbed (Fig. 1). There was no further rectal bleeding, and the patient went on to an uninterrupted recovery. A spontaneous tarry stool occurred two days following proctoscopic examination, at which time the patient was dismissed in satisfactory condition. When seen for follow-up examination six weeks post partum, she was without complaints, and bowel function was normal. The episiotomy was well healed, and bimanual examination disclosed normal findings. The vaginal tract was intact, and no granulation tissue was observed at any point along the vaginal portion of the episiotomy scar. Anorectal examination revealed no primary cause of the severe postpartum rectal hemorrhage.

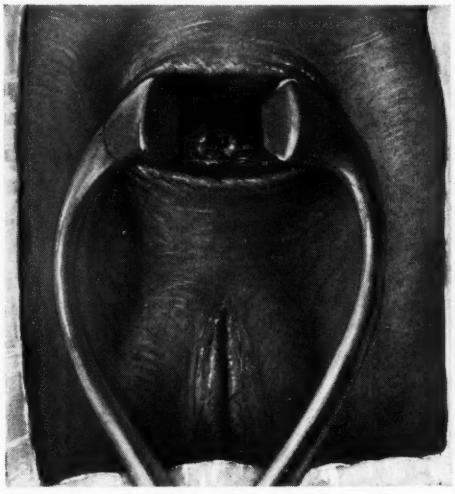

Fig. 1.—Anoscopic view with patient in jackknife position to show shallow ulcer in anterior rectal wall. The source of bleeding may be arterial or venous, and the bleeding point is at the base of the ulcer.

Comment

Rectal hemorrhage in the puerperium is no doubt due to the traumatic events of labor and parturition. What with enemas, repeated digital examinations of the rectum, straining in the second stage of labor, and the possibility of a suture entering the rectum during episiotomy repair, it is remarkable that this complication is not more commonly encountered. That this accident can occur in a patient delivered without episiotomy, laceration, or repair is evident from the experience of Scarborough.[2] He was called in consultation to see such a patient at home on the eighth postpartum day, when she experienced a sudden, massive rectal hemorrhage. His examination disclosed the source of the bleeding to be an arterial spurter on the surface of a large internal hemorrhoid. He inserted a rectal pack and admitted the patient to the hospital, where the bleeding was controlled by transfixing the lesion described above. Recovery was uninterrupted.

The arterial supply of the anal canal and lower rectum is from two sources, inferior hemorrhoidal and branches from the pudendal artery. The venous drainage corresponds. With rectal hemorrhage in the puerperium as with posthemorrhoidectomy hemorrhage, it is often impossible to tell whether the bleeding is arterial or venous in a given instance, although arterial bleeding is usually more profuse. It is conceivable that a thrombosed hemorrhoidal vein could suddenly rupture during the puerperium, giving profuse rectal hemorrhage. It is understandable how a suture in the rectovaginal septum which includes a hemorrhoidal artery or vein could give way between the seventh and tenth days post partum. Unless obliterative endarteritis or secure thrombosis had occurred, rectal hemorrhage would be inevitable.

The symptom of sudden profuse rectal hemorrhage in the puerperium calls for immediate hospitalization for blood replacement and suture of the bleeding point in the rectal

wall. This is best carried out with the patient in the jackknife position, under minimal low spinal anesthesia. The bleeding point is transfixed with No. 0 plain catgut on a small round needle, as in posthemorrhoidectomy hemorrhage, and a strip of Gelfoam may be laid over the operative wound. Access to the field is greatly facilitated by the use of the Newton Smith operating anoscope.

Summary

Severe rectal hemorrhage in the puerperium due to a bleeding point in the anterior rectal wall has been reported. This complication results from rectal trauma during labor and parturition, and may occur without suture penetration of the rectum. Treatment consists of adequate blood replacement and transfixing the bleeding point in the rectal wall.

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EXTRAUTERINE PREGNANCY COMPLICATING TUBERCULOUS SALPINGITIS

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EXTRAUTERINE pregnancy complicating tuberculous salpingitis is an uncommon pathologic condition. Kistner, Hertig, and Rock[1] found only 41 recorded cases up to 1951. They added a single case, and Stoddard[2] in the same year added another. From 1936 to 1952, 300 patients with tubal pregnancies have been operated upon in the Temple University Hospital. During that same period of time, tuberculous salpingitis was diagnosed 26 times. In only two of these patients have the lesions been coexistent. Because the combination is so unusual, these two cases are being reported.

Case 1.—H. D. (Hospital No. 143886), a 28-year-old, married, white, gravida 0, was first seen in the Temple University Hospital on March 3, 1949, with the chief complaints of severe lower abdominal pain, vomiting, and fainting. The menstrual periods had begun at the age of 13 and the menses occurred regularly at 28 day intervals and lasted from 3 to 4 days. During the two years prior to admission, the patient had noted several transient attacks of midabdominal pain and gaseous distention unrelated to the menses. She had been trying for several years to become pregnant. The last normal menstrual period began on Jan. 7, 1949, and in February she experienced some nausea, but there were no other symptoms suggestive of pregnancy. On the morning of admission to the hospital she experienced a severe left lower quadrant pain with which she "doubled up" and following which she vomited and fainted. There was no associated vaginal bleeding.

Physical examination revealed a patient in acute distress with a temperature of 97° F., pulse rate 100, and blood pressure 120/70. The abnormal findings were confined to the abdomen and the pelvis. The abdomen was slightly distended below the umbilicus and very tender to palpation. There was marked rebound tenderness over the entire lower abdomen. On pelvic examination the corpus of the uterus was palpable anteriorly and was slightly enlarged and softened. The posterior cul-de-sac was filled with a tender, soft mass suggesting a hematoma. There was no palpable adnexal enlargement. Hemoglobin was 11 Gm., the red blood cell count 2.5 million per cubic millimeter, and the white cell count 23,900 per cubic millimeter.

At operation the abdomen contained approximately 2,000 c.c. of fresh blood and clots. Both tubes were enlarged and clubbed, and a large blood clot and fragments of placental tissue were protruding from the fimbriated end of the left tube. There was profuse bleeding from the raw surfaces. The fimbriated end of the right tube was closed. The ovaries were normal in appearance and there were multiple adhesions between the bowel and the broad ligaments. Since the patient was in good condition at this time and because of her desire for pregnancy, a right salpingostomy was done after the left tube had been removed.

Microscopic examination revealed the following: "Within the lumen of the tube and replacing its mucosal surface are sheets of decidual cells and cross sections of chorionic villi which are punctuated by blood clot. Multiple sections of the Fallopian tube reveal numerous collections of mononuclear cells which have an epithelioid pattern highly sug-

gestive of tuberculosis. Kinyoun's stain is positive for tubercle bacilli.'' A diagnosis of ectopic pregnancy and tuberculous salpingitis was made.

The immediate postoperative course was uneventful and a chest x-ray was negative. Following discharge from the hospital, the patient developed abdominal pain and distention and was again hospitalized from July 6, 1949, until Aug. 5, 1949, for the treatment of tuberculous peritonitis with ascites. Kinyoun's stain on the peritoneal fluid revealed tubercle bacilli. Over a 62 day period she received a total of 53 Gm. of dihydrostreptomycin without reaction. She remained asymptomatic until Dec. 26, 1949, at which time she was readmitted with symptoms suggestive of a partial bowel obstruction. This responded to treatment with intestinal intubation and at the time of discharge from the hospital, pelvic examination revealed only cul-de-sac tenderness. The menses since then have been normal and the patient has resumed her usual activities.

CASE 2.—E. W. (Hospital No. 171569), a 28-year-old, married, white, gravida 0, was first seen on July 2, 1951, complaining of pain with defecation. The menstrual periods had begun at the age of 14 and occurred regularly at 28 day intervals lasting 6 days. She had been told as a child that she had a ''spot'' on her lung, but repeated chest x-rays had shown no evidence of infection.

The last normal menstrual period had begun on April 25, 1951, and in May, 1951, the patient noted swelling of the breasts, morning nausea, and urinary frequency. On June 8, 1951, she experienced lower abdominal cramping pain associated with vaginal spotting. She was admitted to another hospital on June 15, 1951, and was discharged four days later with a diagnosis of intrauterine pregnancy. The hemoglobin was 10.5 Gm. The white blood cell count was 8,500 per cubic millimeter, the red blood cell count, 3.59 million per cubic millimeter, and a pregnancy test was positive. After her discharge from the hospital the cramping lower abdominal pain and spotting continued and on June 26, 1951, the patient noted severe abdominal pain during defecation. In the following week she fainted several times while attempting to empty the bowel. The vaginal spotting persisted, but the breast and urinary symptoms subsided.

Upon her admission to the Temple University Hospital the temperature was 99° F., the pulse rate 80, and the blood pressure 110/70. Positive physical findings were confined to the abdomen and pelvis. There was moderate tenderness in the left lower quadrant of the abdomen with muscle guarding and mild rebound tenderness; peristalsis was normal. On pelvic examination, dark blood was noted to be coming from the cervical canal. The corpus of the uterus was small and anterior. A 7 cm. tender, doughy, fixed mass was palpable in the left adnexa, extending posteriorly into the cul-de-sac. The right adnexal area was normal to palpation. The hemoglobin was 10 Gm., the red blood cell count 3.6 million per cubic millimeter, and the white blood cell count 8,650 per cubic millimeter.

A diagnosis of left tubal pregnancy with pelvic hematocele was made, and on June 2, 1951, a needle colpotomy was productive of dark red blood from the posterior cul-de-sac. The abdomen was then opened and the entire pelvis was found to be the site of an organized hematoma throughout which were scattered fragments of placental tissue. The left tube was dilated in its distal third and the fimbriated end was covered with a mass of blood clot and placental tissue. The distal half of the right tube was dilated to twice normal size and covered with blood clot and necrotic-appearing tissue. No perforation of either tube was noted. The ovaries were not adequately visualized because of the excessive reaction in the cul-de-sac and the broad ligaments. A left salpingectomy was performed.

Microscopic examination of the tissue revealed the outer portion of the tube to show fibrous thickening and clotted blood. ''Swollen, pale cells with a decidual pattern and chorionic villi are present in the clot. Infiltrating the mucosa are multiple granulomata composed of epithelioid cells and lymphocytes accompanied by giant cells of the Langhans' variety and caseation necrosis. Kinyoun's stain is negative for acid fast organisms.'' The diagnosis of ectopic pregnancy and tuberculous salpingitis was made.

The postoperative course was uneventful and a chest x-ray was negative. Following discharge from the hospital, the patient was given dihydrostreptomycin, 1 Gm. twice weekly, and para-aminosalicylic acid, 12 Gm. daily over a 13 week period. An endometrial biopsy done on Oct. 1, 1951, disclosed chronic granulomatous endometritis, but Kinyoun's stain was negative for acid fast organisms. Normal secretory endometrium was reported after a second endometrial biopsy on Dec. 12, 1951. At the present time the patient is asymptomatic with normal periods and no palpable pelvic pathology.

Summary

Two patients with chronic tuberculous salpingitis who developed tubal pregnancies were presented. In one, tuberculous peritonitis followed the operative procedure, but she is now asymptomatic following treatment with dihydrostreptomycin. The second patient was started on treatment with dihydrostreptomycin and para-aminosalicylic acid immediately after operation, and at the present time is asymptomatic and has no evidence of infection.

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THECOMA ASSOCIATED WITH ADENOCARCINOMA OF THE ENDOMETRIUM

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IN THE 20 years since the first description of the thecoma of the ovary, by Löffler and Priesel[1] in 1932, there has developed increasing interest in the relationship of both feminizing mesenchymoma of the ovary as well as ovarian stromal hyperplasia, to both endometrial hyperplasia and finally adenocarcinoma of the endometrium.

A rather complete summary has recently appeared by Ingram and Novak[8] with the comment that although granulosa-cell tumors are about ten times as common as thecomas, yet 28 thecomas have been reported in association with adenocarcinoma of the endometrium, whereas only 22 granulosa-cell tumors have been similarly reported.

The purpose of this report is to add a case report of thecoma, possibly bilateral, associated with adenocarcinoma of the endometrium. This case is particularly interesting in view of the fact that, while in the largest reported series, that of Woll, Hertig, and associates[7] listing 17 cases, the authors did not mention the occurrence of bilateral tumors specifically, yet they did state that in cases of adenocarcinoma of the endometrium, 56 to 92 per cent of the ovaries show stromal hyperplasia.

Case Report

This 64-year-old white woman was admitted to the hospital on Oct. 19, 1949, with a history of vaginal discharge and spotting intermittently for 8 months, the discharge becoming gradually more brownish and being associated with a bandlike fullness across the lower abdomen. Her weight was 155 pounds and there had been no recent loss. The patient had had no pregnancies. Menstrual periods were normal until the menopause, which occurred without complications at the age of 47.

Pelvic examination was essentially negative, except for slight enlargement of the uterus, which was in a position of first-degree retroversion.

A dilatation and curettage on Oct. 20, 1949, showed a considerable amount of friable endometrium, with a rapid frozen section diagnosis of adenocarcinoma, Grade II. Total hysterectomy with bilateral salpingo-oophorectomy was done the same day. Gross pathological examination of the specimen (Fig. 1) showed a 10 by 5 by 4 cm. uterus with a markedly hemorrhagic endometrial cavity containing a grayish-brown tumor area in the fundus, 3 by 2.5 cm., penetrating about 1 cm. into the myometrium. The right ovary measured 3.5 by 2 by 2 cm. Section showed it to consist almost entirely of firm yellowish tissue. Section of the left ovary, 3 by 2 by 1.5 cm., showed a fairly well circumscribed yellowish tumor, which shelled out easily, about 1.5 cm. diameter.

Microscopic sections of the endometrium (Fig. 2) showed adenocarcinoma, Grade II. Sections of the tumor in the left ovary showed hyperchromatic vesicular nuclei (Fig. 3). Scharlach R fat stain revealed marked lipoid deposits in the cytoplasm. Sections of the right ovary showed a marked stromal hyperplasia, some fields with large cells, hyperchromatic, vesicular nuclei, and lipoid deposits in the cytoplasm (Fig. 4). A recent communication from

Dr. Novak and the Registry of Ovarian Tumors of the American Gynecological Society states that the tissue from the right ovary may represent a marked stromal hyperplasia, although there are areas in which the microscopic cell characteristics and pattern would certainly suggest a thecoma.

There was no evidence of metastasis either of the ovarian tumor or of the adenocarcinoma. Follow-up for three and one-half years indicates no demonstrable evidence of recurrence of either tumor.

Fig. 1.—Gross specimen showing adenocarcinoma of the endometrium with bilateral ovarian thecomas.

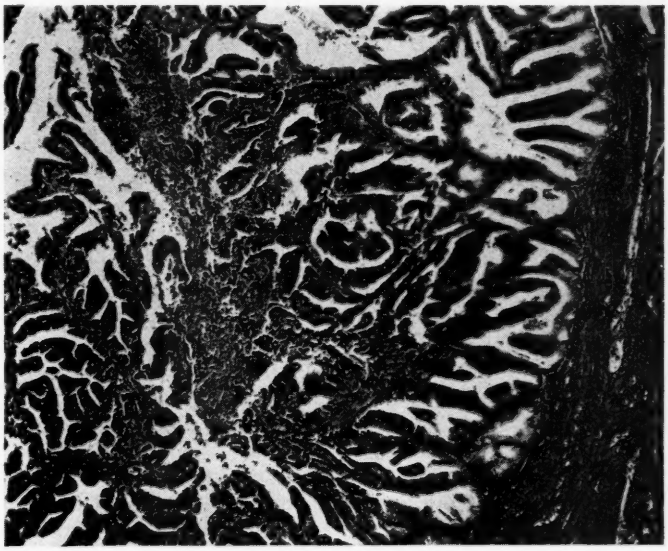

Fig. 2.—Microscopic section of endometrium showing adenocarcinoma.

Comment

In the entire series previously reported of thecoma of the ovary associated with adenocarcinoma of the endometrium (26 cases), as well as in the present case, the diagnosis of ovarian pathology has never been made prior to surgery, as far as we have ascertained.

In view of the findings by Woll, Hertig, and associates,[7] showing ovarian stromal hyperplasia in 56 to 92 per cent of adenocarcinomas of the endometrium, as well as an incidence of thecoma 9 times as great as that normally expected, it is still certainly not conclusive which is the forerunner, the adenocarcinoma or the ovarian tumor.

Fig. 3.

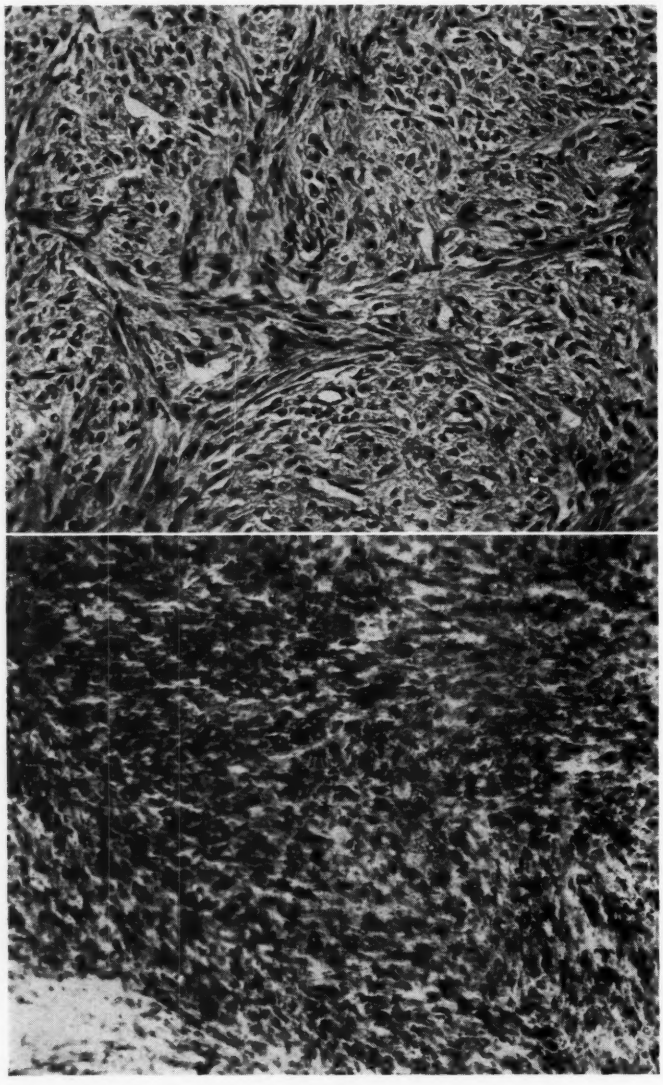

Fig. 4.

Fig. 3.—Microscopic section of the left ovary.
Fig. 4.—Microscopic section of the right ovary.

In this case, if the original tumor is the thecoma of the left ovary, with estrogen production, one might expect the other ovary to be suppressed by the hormone and give an atrophic appearance. If there is an element in the adenocarcinoma of the fundus which produced the ovarian hyperplasia, then one might expect both ovaries to be stimulated, which is what has occurred in this particular patient.

Conclusion

A case of thecoma of the ovary, possibly bilateral, associated with adenocarcinoma of the endometrium, has been presented, with a few comments about previously reported cases. We feel there is a probable hormonal interrelationship in the simultaneous development of the two entities.

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HEMANGIOENDOTHELIOMA OF THE VAGINA

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HEMANGIOENDOTHELIOMA is a rare type of malignant neoplasm of vascular origin. This tumor occurs in a wide variety of sites, most commonly the mammary glands, liver, bones, skin, and subcutaneous tissues, and female internal genitals. Although the total of reported cases probably does not exceed 30 to 40, actual instances are undoubtedly more numerous.

According to Stout,[1] there are two criteria for recognition of this neoplasm. "These are, first, the formation of atypical endothelial cells in greater number than are required to line the vessels with a simple endothelial membrane; and, second, the formation of vascular tubes with a delicate framework of reticulum fibers and a marked tendency for their lumens to anastomose. The variations found are due to the marked variability in the number, shape, size and tinctorial peculiarities of the malignant endothelia."

The vascular nature of these tumors is manifested by their clinical behavior. They present a definite and often alarming tendency toward either interstitial or external hemorrhage. Once the tumor penetrates to a surface where it can be subjected to trauma, exsanguination is a possibility.

The aggressive potentialities of the hemangioendothelioma vary considerably. Of the 18 patients in Stout's series, 10 died with metastases in the period from 2 months to 20 years following discovery of the initial lesion. The sites of metastatic involvement include the lungs, heart, abdominal viscera, bones, and skin, spread occurring through both vascular and lymphatic channels.

The treatment of hemangioendothelioma is by surgery and/or irradiation. Based upon reported cases the cure rate by either method or combination is far from satisfactory. In Stout's series all but one were treated exclusively by surgery. Ten of these died within 5 years of operation with cure in doubt in the remaining eight. In the one instance where roentgen therapy was employed as an adjunct to surgery, it apparently added nothing to the longevity of the patient. Bowing, Fricke, and McClellan[2] report on 4 cases of hemangioendothelioma of the uterine cervix in which one of this group was subjected to a total abdominal hysterectomy with a 5 year survival. The remaining 3 patients received x-ray and/or radium therapy. One succumbed 6 months after treatment. The second was alive 2 years after treatment. The third died 7½ years after initial diagnosis presumably from cardiovascular disease. Another case of hemangioendothelioma of the pelvis was reported by Rubin and Dann.[3] Their patient was treated by external roentgen therapy following an unsuccessful exploratory procedure. This patient was alive and well 12 years following diagnosis.

Case Report

D. Q., an 18-year-old woman, was first seen by her physician in February, 1948, because of intermenstrual bleeding. Past medical, surgical, and menstrual histories were entirely negative. Physical examination disclosed the uterus to be small and anterior in position. The cervix was normal in size and appearance. No masses were found in the adnexa on either side. A 1 by 1 by 0.3 cm. ovoid sessile mass with ulcerated purplish

surface was found in the left lateral vaginal fornix. This mass was excised by sharp dissection on March 22, 1948. The pathological report was hemangioendothelioma (Fig. 1).

The patient was asymptomatic until 7 months later, Oct. 17, 1948, when metrorrhagia again occurred. Examination revealed local recurrence. This was excised and coagulated with good immediate results. Several follow-up studies, including one in August, 1950, almost 2 years later, showed no reappearance of the tumor.

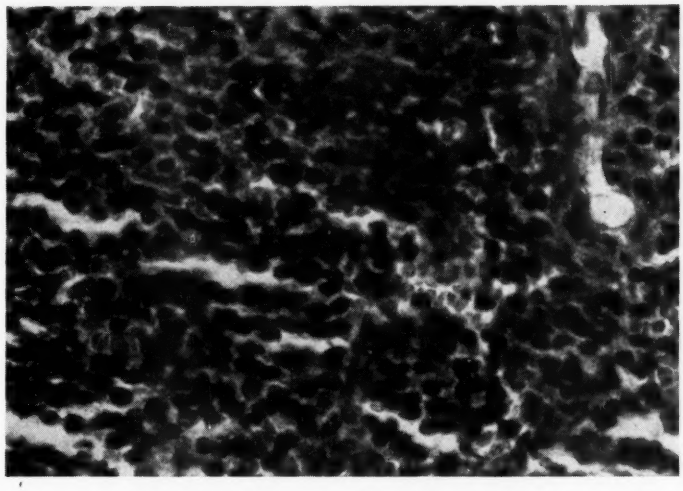

Fig. 1.—Hemangioendothelioma of vagina. Closely packed, fairly uniform endothelial cells surrounding numerous tiny vascular spaces.

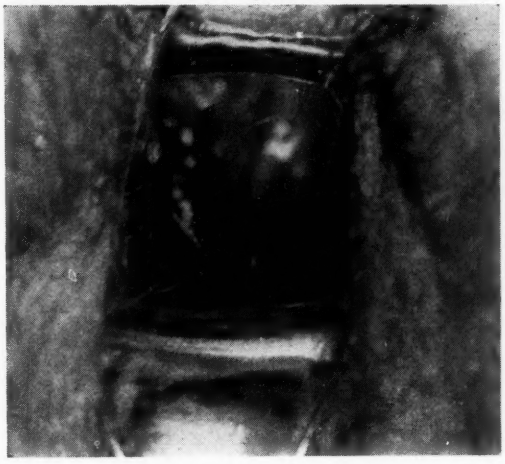

Fig. 2.—Intravaginal mass obscuring cervix and filling vaginal vault.

The patient was married in May, 1951. Following coitus, profuse vaginal bleeding occurred. The patient was then hospitalized for study and further treatment. Physical examination revealed a sanguineous vaginal discharge. The cervix was displaced posteriorly and hidden by a bluish-purple soft, polyplike tumefaction which measured 5 by 5 by 7 cm. in dimensions. This mass was freely movable and bled readily (Fig. 2). No definite adnexal masses could be felt although the lateral vaginal fornices appeared to be involved by additional deposits of tumor tissue.

Upon consideration of the patient's age and status, the type of operation indicated, etc., it was felt that a course of external roentgen therapy was advisable, especially in view of the reported radiosensitivity of this tumor. This was accordingly begun on May 26, 1951, and completed 3 weeks later on June 19, 1951. The Marks grid method[5, 6] with 40 per cent open area, 15 by 15 cm. anterior and posterior pelvic fields, 200 KVP, Hvl 1.1 mm. Cu, 50 cm. F.S.D. was employed. A daily dose of 900 r (air) was administered to alternate areas. Treatment was given daily except Saturday and Sunday. A tumor dose of 4,000 r was attained although it was originally planned to reach 6,000 r. Treatment had to be curtailed at the lower level due to difficulties in placement of the grid because of the curved surfaces and folds in the inguinal and gluteal regions. Intravaginal roentgen therapy was considered at this point to augment the dosage already delivered, but this was refused by the patient. The skin reactions which ensued reached second degree in most areas but finally healed within 2 months after the last treatment visit. The response of the tumor was remarkable. It proved to be very radiosensitive. Two months after completion of roentgen therapy, pelvic examination was entirely within normal limits. A Schiller test of the cervical mucosa disclosed normal reaction. The patient's general condition was good. Her menstrual periods had ceased. Follow-up study was likewise normal.

Fig. 3.—Intravenous urography, 5 minute film. Normal right urinary tract, nonfunctioning left kidney.

Reappearance of vaginal bleeding was noted on March 7, 1952. Examination at this time disclosed an ulcerating tumefaction in the left lateral vaginal fornix 1 by 1 by 0.2 cm. in dimension with a mass in the left parametrial region. Some weight loss was evident. The patient was pallid. Admission x-ray of the chest disclosed no evidence of pulmonary metastases or pleural abnormality. Intravenous urography revealed a nonfunctioning left kidney (Fig. 3). Barium enema examination disclosed pressure on and displacement of the sigmoid colon without definite evidence of infiltration by a pelvic tumor (Fig. 4). Cystoscopy revealed a stricture 2 cm. proximal to the left ureterovesical junction. A No. 4 catheter was passed after some difficulty into the left renal pelvis for drainage purposes. A dye function test of the left urinary tract later showed very poor excretion. Retrograde urographic study subsequently revealed mild caliectasis in the left kidney.

Pelvic exploration through a low midline incision was attempted on March 25, 1952. The uterus, tubes, and ovaries were found to be small, atrophic, and not involved by tumor tissue. In the left pelvis there was a tumor mass about 5 cm. in diameter extending into the left broad ligament and anterior fossa, and adherent to the sigmoid colon. Similar tumor tissue was found overlying the anterior aspect of the sacrum extending cephalad to the promontory. Marked vascularity of the tumor masses in addition to their pelvic distribution rendered surgical excision too hazardous. No further operative procedures were therefore attempted. The hepatic, renal, and para-aortic areas appeared to be free of metastases.

The postoperative period was complicated by a severe paralytic ileus secondary to intra- and retroperitoneal bleeding. A left pyelonephritis developed which was recalcitrant to usual therapy. The patient lost further ground. Pulmonary metastases were subsequently demonstrated. Death occurred 4 years and 3 months following the first symptoms.

Fig. 4.—Barium enema examination, spot film (retouched), left posterior oblique projection. Pressure effect on sigmoid colon by adjoining mass in left fornix.

Comment

The tendency to recurrence following local surgery of the type illustrated in the reported case is an important clinical feature of hemangioendothelioma. This characteristic has been emphasized by Drucker,[4] who further noted that the addition of irradiation to the treatment program apparently tends to minimize the frequency of local regrowth.

In evaluating a plan of treatment for this neoplasm, it must be remembered that those cases reviewed in the literature antedate the modern period of "radical" surgery. Similarly, radiation therapy as described does not conform with present standards of exactness in dosage statement. Such physical information as is available is inadequate in many instances for analysis. One must therefore conclude that the treatment of hemangioendothelioma is still in an indeterminate phase. If encountered, radical extirpation by surgery and/or radiation therapy should be considered in view of the frequent failure of less thorough measures in the past.

Conclusions

1. Hemangioendothelioma of the vagina is a radiosensitive but not necessarily radiocurable neoplasm.

2. Early recognition with immediate institution of radical therapeutic measures, surgery and/or irradiation, is essential to cure if this is to be achieved in a significant percentage of patients.

3. A case of hemangioendothelioma is presented.

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CERVICITIS RESULTING FROM TURPENTINE IRRITATION*

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A 20-YEAR-OLD gravida ii, para ii, Negro woman was admitted to Milwaukee County General Hospital from Milwaukee Emergency Hospital with the diagnosis of pelvic inflammatory disease and acute lordosis. At the time of admission to Milwaukee County General Hospital she complained of a severe pain in the right lower quadrant. She had a foul-smelling vaginal discharge. A mild discomfort in the right lower quadrant had been present eight days before admission. This gradually increased in severity necessitating her being confined to bed for three days preceding admission. The foul-smelling white vaginal discharge had been noticed the week prior to admission. Postcoital spotting had occurred for a month. She complained of dyspareunia, and had episodes of fever and chills. Her menstrual history was normal. The last normal menstrual period was nine days before admission. She had been separated from her husband and children for a year and lived with a brother who died of tuberculosis.

Physical Examination.—

Oral temperature was recorded at 99.2° F. Physical examination was within normal limits except for several large, hard, movable nodes in the right inguinal area. The vagina revealed a moderate white, foul-smelling discharge. On visualization of the cervix a red, raised, granular lesion measuring 3 cm. in diameter was observed on the right side of the cervix. When sponged, this lesion bled freely. Biopsy and smear were taken at the time of examination. Chest x-ray taken the day following admission was negative. The white blood count was 20,700. The sedimentation rate was 65/96.

Two days following admission the Pathology Department reported that the biopsy was predominantly granulation tissue accompanied by an intense inflammatory reaction in which there were numerous eosinophils and plasma cells. The impression was venereal disease, probably a primary syphilitic lesion of the cervix. Dark-field examinations of the lesion and inguinal nodes were negative. Kline, Eagle, and Wassermann tests were negative. The Frei test was negative, the Mantoux test was read as two plus.

After seven days of hospitalization the diagnosis remained primary syphilitic lesion of the cervix. Fourteen days following admission after repeat biopsy and photographs, the patient, noticing the special attention she was receiving, wrote a note hoping it would aid in the diagnosis. This revealed that she had had violent intercourse a month before the onset of the present episode. Having severe pain after this episode she used a "family remedy douche" consisting of alum and petrolatum in turpentine.

Sixteen days following admission the report of the second biopsy read as follows:

"The fragments of cervical tissue show ulceration of the overlying squamous epithelium which is irregularly thickened. The base of the ulceration consists of a very thick layer of fibropurulent material covering a rather cellular inflammatory zone, consisting mainly of lymphocytes, plasma cells, and large numbers of histiocytes, some of which are fat laden. There is no specific character to the nature of the inflammatory process or histologic changes involving the surrounding supportive tissue. Giemsa and Gram stains of the tissues reveal no significant microbiologic organisms. Animal inocula-

*Presented at a meeting of the Chicago Gynecological Society, Jan. 16, 1953.

tions of a fragment of the submitted tissue resulted in death of the animals with no specific gross pathological changes. Bacteriologic studies are still being carried out with results pending.

"*Diagnosis:* Nonspecific chronic inflammation of the cervix with surface ulceration."

Three weeks after admission no definite diagnosis had been made and the lesion persisted. The slides were then submitted to the Tissue Seminar at Marquette University School of Medicine. After presentation of the case history and slides Dr. Birge, Pathologist at Milwaukee Hospital, recognized the lesion. He had had a similar slide from a home for unwed mothers. In this case the girl had used a turpentine douche in an attempt to abort herself and in a like period of time developed a cervical lesion with similar gross and microscopic appearances.

The patient was dismissed, having received only supportive therapy while awaiting diagnosis, and followed at the Milwaukee County Dispensary. Six weeks after dismissal she was re-admitted to Milwaukee County General Hospital for re-examination and treatment. The lesion had persisted and retained its original characteristics both gross and microscopic. Cautery was used as the treatment of choice and she was dismissed. Five weeks after cautery the cervix was clean and well healed.

Summary

Two cases demonstrating similar characteristic lesions of the cervix caused by turpentine used in douche preparations are described.

Lesions of this nature must be differentiated from carcinoma of the cervix, syphilitic lesions of the cervix, and tuberculosis of the cervix.

A careful review of the literature failed to reveal any reports of lesions of a like nature.

AN OVARIAN DERMOID CYST WITH NUMEROUS SEBUM BALLS

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OF THE teratomas of the ovary, the dermoid cyst is the most common and occurs 120 to 200 times as frequently as the solid embryoma.[1] It comprises about 12 per cent of all ovarian tumors and usually occurs in younger women. In 2 to 15 per cent of the cases, the cyst is bilateral. They usually have a thick, dull capsule with a whitish skin-like inner lining. Intracystic plugs arise from the cyst walls, in every instance.[2] They may appear as small warty projections, protruding slightly into the cavity, and are discovered only by careful examination, but more often they appear as nipplelike projections covered by white opaque hairy skin which is often shaggy. Though ectodermal elements are predominant structures, tissues derived from mesoderm and entoderm are sometimes noted.

The contents consist of an oily pultaceous material composed of sebaceous and sudoriferous secretions with desquamated epithelium and occasionally teeth. This oily substance is fluid at body temperature and solidifies upon cooling to room temperature.[1]

The purpose of this paper is to report a large dermoid cyst filled with 250 round sebum balls. This is the only such case I have observed in 150 dermoid cysts of the ovary examined.

Case Report*

I. F., a 53-year-old Italian woman, was admitted to the hospital with sudden abdominal pain and nausea. About five years before admission, she began to notice slight fullness in the abdomen, with increasing distention associated with frequent belching. Previous to the menopause a few years ago, her periods were regular. Following the menopause, there was a continuous mucous vaginal discharge. She was married at the age of 22 and had 6 children, 4 of whom are living. An appendectomy was performed many years ago. Her bowel habits and nutrition were normal.

Physical examination disclosed a well-developed and nourished 53-year-old white woman who complained of severe pain over the entire abdomen. The heart was slightly enlarged with good regular beats and no murmurs. The blood pressure was 196/140 and the temperature was normal. The abdomen was distended and a solid tender mass about the size of an 8 months' pregnancy filled the entire pelvis as high up as the umbilicus. It appeared firm, ovoid, and somewhat movable. Vaginal examination disclosed a large firm mass which was diagnosed as an ovarian cyst. There were many varicose veins of the lower extremities.

X-ray examination revealed the presence of a tremendous, rather ill-defined homogeneous mass filling the entire pelvis and extending upward from the midline over toward the right lower and midabdominal quadrants. The shadow was of a ground-glass appearance, ill defined, and contained no specific calcific deposits within its confines. The diagnosis of choice was a tremendous ovarian cyst.

Laboratory examination showed 5.25 million erythrocytes with 14.5 Gm. of hemoglobin and a white cell count of 12,200 with 87 per cent segmented cells and 13 per cent lymphocytes.

*Case of Dr. A. M. DeAngelis.

An operation was performed on the third hospital day and a large twisted dermoid cyst arising from the left side was removed. Her short course in the hospital was uneventful.

Gross Appearance of the Tumor (Fig. 1).—The specimen consisted of a large ovarian dermoid cyst 17 cm. in diameter, perfectly symmetrical, and covered by a thick, opaque, pinkish-gray, drumlike capsule. The inner surface was lined by a thick white skinlike membrane which appeared cracked at several places. A careful search disclosed a small conelike elevation of about 2 cm. and 1 cm. at the base. The contents consisted entirely of approximately 250 gray, puttylike balls, each 2 cm. in diameter and uniform. On closer examination, these balls were butterlike in consistency and most of them had only one hair situated centrally and extending outward.

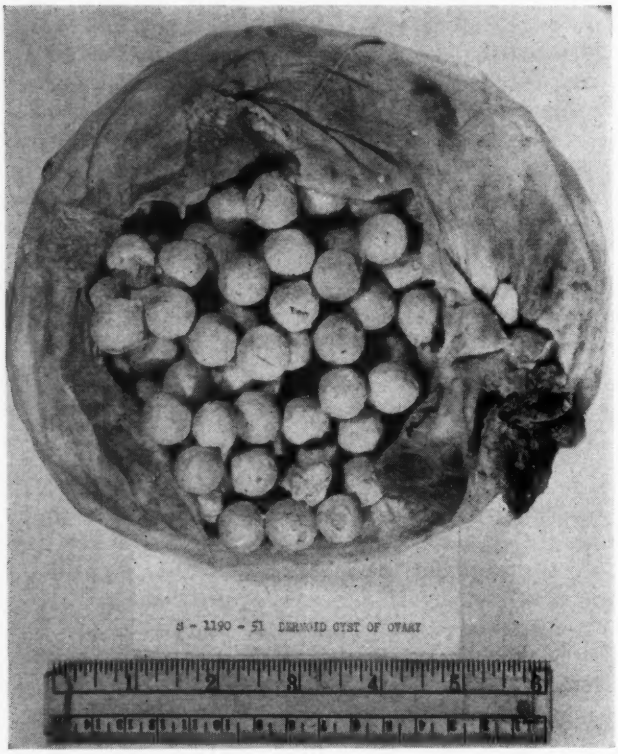

Fig. 1.—Ovarian dermoid cyst with numerous sebum balls.

Microscopic Section.—Sections taken through the knob and the wall disclosed an epidermal lining of well-oriented stratified squamous epithelium with numerous sebaceous and sudoriferous glands.

Comment

I am aware of only a few similar cases reported in the literature. Willis[3] described one large bilocular "dermoid" removed surgically from a 57-year-old woman, which was lined by skin and contained teeth and 2 gallons of sebaceous fluid in which were suspended 1,800 "butter balls," each about 1.5 cm. in diameter, and a few larger hairy balls. Also, according to Willis, the contents of huge cysts sometimes form a multitude of spherical firm butter balls, doubtless from mechanical agitation.

Bland-Sutton[4] depicted a dermoid cyst containing 3,930 sebum balls.

Barzilai[2] states that the sebaceous and horny material occasionally becomes worked up into pellets and the hair may form balls and small wisps.

Ewing[5] states that sebaceous or oily material is mingled with hair. It may be condensed in the form of firm globules, or be in a large mass consisting of fatty crystals forming about hair, or in epidermal concretions. The occurrence of these masses has been attributed to albuminous bloody exudate following torsion, to mixture with secretion from sweat glands, or to a sort of butter formation.

Bonney[6] counted 4,000 small globules in one case, and Opitz[7] reports their appearance in stools through an intestinal fistula.

Summary

An unsual dermoid cyst of the ovary containing 250 sebum balls which occurred in a 53-year-old Italian woman is reported. Only a few such cases have been reported in the literature and mention is made of them in this article.

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VAGINAL ELEVATOR FOR ABDOMINAL HYSTERECTOMY

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MOST surgeons who perform total abdominal hysterectomies have occasional difficulty in incising into the vaginal vault at the right level. Sometimes dissection is carried too far past the anterior fornix and bothersome bleeding from the bladder and vaginal venous plexuses is encountered. At times the opening is made too high, resulting in the incision of the cervix instead of the vaginal fornix. Another error lies in incising the vagina too low so that valuable anterior vaginal mucosa is lost and the vagina shortened. Frequently time is lost in opening the vagina correctly even if the incision is properly made. Several years ago we devised a special instrument to eliminate these difficulties.

The instrument is a simple one which was first made from a laparotomy tape ring and the handle of an adenoid retractor. The ring is 2 inches in diameter and the handle is 8½ inches long (Fig. 1).

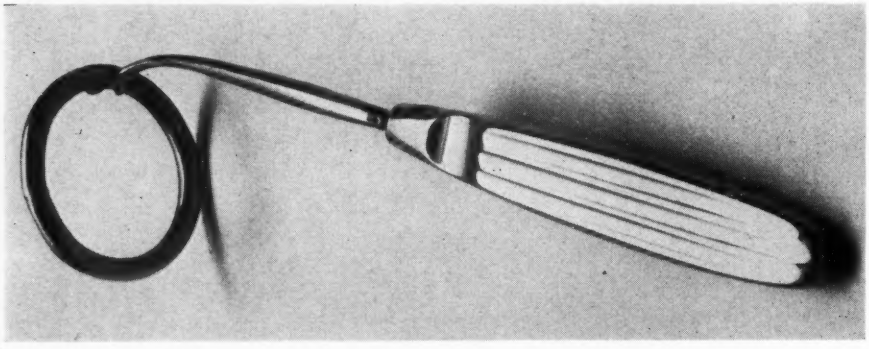

Fig. 1.

Technique

Prior to the abdominal procedures, perineal and vaginal preparation is performed, a Foley catheter is inserted, and the vaginal elevator put in place. The ring of the elevator is inserted through the vaginal orifice in a manner similar to the insertion of a pessary, and then advanced along the anterior wall of the vagina, the handle following the posterior wall of the vagina. Proper position of the handle can easily be determined by the feel of the grooves on the ring side.

The operation is begun and the elevator is left in place. When the hysterectomy has advanced to the time for the vaginal opening, the nurse makes gentle pressure cephalad on the handle of the elevator from below. This clearly outlines the top of the anterior vaginal fornix. The fornix is then opened with a scalpel over the ring and Allis clamps are applied to the sides of the vaginal incision.

The elevator is withdrawn from below and a Zephiran sponge is inserted into the vagina. In opening the remainder of the vagina, curved Mayo scissors are used. These are inserted with the scissors parallel to the mucosa so as to leave as much of the vagina as possible.

We have employed the above procedure using the vaginal elevator in 160 cases and have yet to encounter an unsuccessful one. Since the ring does not actually fit over the cervix but merely indents the anterior fornix, its size has been adequate in all cases. It is conceivable that one might find a case where the vaginal orifice is too small to admit the ring.

This instrument may also prove valuable in outlining the vaginocervical junction during surgery for early carcinoma of the cervix, enabling the surgeon to avoid cutting into the tumor.

STILBESTROL TREATMENT OF ENDOMETRIOSIS

Report of a Case

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IN THE past few years stilbestrol has been used widely in the treatment of endometriosis. If stilbestrol causes atrophy and disappearance of ectopic endometrial growths, an important method of treatment is available. This case report is recorded with microscopic studies for consideration with other carefully studied cases.

Karnaky[1] first advocated the use of stilbestrol in the treatment of endometriosis in 1948. He reported 37 cases, including 3 with endometriosis in laparotomy scars, 4 involving the posterior vaginal fornix, and 3 diagnosed by biopsy at laparotomy. Large amounts of stilbestrol were advised, the dosage increasing from 0.5 mg. daily to produce amenorrhea. If bleeding occurred during therapy, it was controlled by an increase in the administered stilbestrol up to 250 mg. or more daily. In no case was there evidence of growth of the endometrial implants, nor were the symptoms made worse during or after stilbestrol therapy. Apparently, cysts and adenomyomas in the cul-de-sac disappeared or became smaller. Symptoms usually disappeared. Five patients subsequently became pregnant.

Bickers[2] reported 19 cases of extensive endometriosis treated with stilbestrol, 5 mg. daily from the fifth to the twenty-fifth day of the cycle for three consecutive months. The results were considered excellent with recurrence in only 2 cases.

Hurxthal and Smith[3] in 1952 reported on 28 patients with endometriosis treated with stilbestrol. One had continuous treatment producing amenorrhea over five years. Occasionally during this time the drug was discontinued but painful menstruation recurred. In the second there was improvement for several years and then periodic bleeding and increased pain returned. At operation no endometriosis was found. A third patient became pregnant after taking small doses of stilbestrol. Of the remaining 25 cases pain was completely relieved in 4, markedly decreased in 12, and slightly decreased in 8. In 2, painful menses continued although large doses of stilbestrol were given. The 4 patients who were completely relieved of pain received estrogen therapy for protracted periods, and did not menstruate. Three of these had slight vaginal bleeding from time to time. Treatment was discontinued in 7 patients; there was failure to relieve pain in 4, development of swollen labia in 1, marked fluid retention in another, and psychotic symptoms in the last. The authors concluded that stilbestrol may be helpful in endometriosis.

Case Report.—(N-64782) The patient, unmarried, aged 19 years, was first seen Aug. 26, 1946, complaining of severe dysmenorrhea. Her menses began at the age of 12, occurred every twenty-eight to forty days, lasted six days each month with quite heavy flow and clots. For the first year there was no pain. At 13 dysmenorrhea began, increasing in severity, duration one to two days, with radiation of pain to the rectum.

The patient appeared in good health. The hymen was intact. By rectal examination the uterus was small, anterior, and movable. In the cul-de-sac there was nodular thickening extending to each side and into the left uterosacral ligament. The ovaries were not outlined. Small doses of thyroid and simple analgesics were given, but the pain became increasingly severe.

On March 12, 1947, the cervix was dilated and the uterus curetted. A low midline incision revealed the ileum adherent with subacute adhesions between its loops and the tubes, ovaries, and uterus. There was brownish discoloration of the pelvic peritoneum and viscera. Edema suggested a chemical peritonitis with the last menses. The anterior cul-de-sac contained a number of typical endometrial implants. Both ovaries consisted of chocolate cysts, densely adherent, 5 to 6 cm. in diameter. The right ovary was resected, leaving one-third of a normal ovary. The left tube and ovary were excised. There was marked thickening in the cul-de-sac and uterosacral ligaments, grossly characteristic of endometriosis.

Microscopic sections (Fig. 1) of the left ovary showed an endometrial cyst partially lined with columnar cells beneath which there was endometrial stroma.

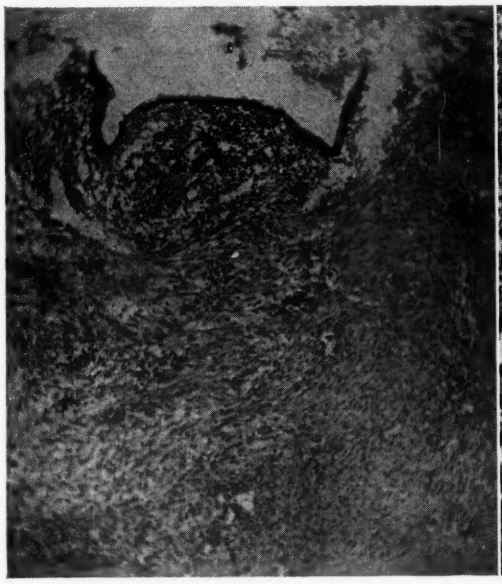

Fig. 1.

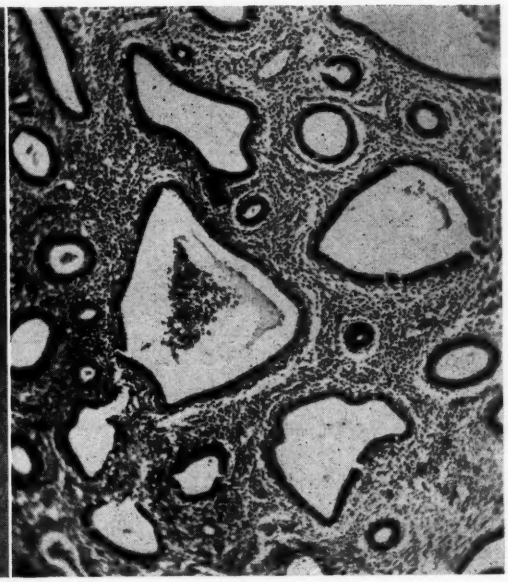

Fig. 2.

Fig. 1.—Endometrial cyst of left ovary, removed before stilbestrol, partially lined with columnar cells beneath which there was endometrial stroma.

Fig. 2.—Endometrium from curettage after ten weeks of stilbestrol. Marked hyperplasia with "swiss-cheese" glands. Patient had hemorrhage for ten days.

Fig. 3.

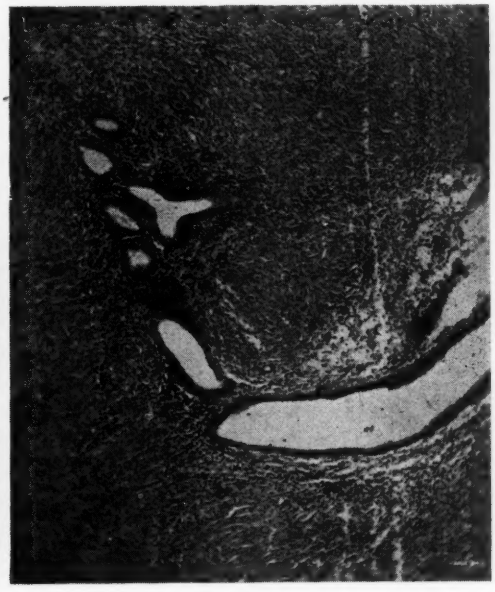

Fig. 4.

Fig. 3.—Endometrium showing hyperplasia after second two months' treatment with stilbestrol.

Fig. 4.—Endometriosis excised between uterus and bladder at second operation. Epithelium hyperplastic with no suggestion of atrophy.

The patient improved after operation but six months later there was increasing dysmenorrhea. After two years of marriage, conception had not occurred; the dysmenorrhea and dyspareunia were so marked that an experimental course of stilbestrol therapy was undertaken. At this time the uterus was of normal size. Marked nodular thickening was present in the cul-de-sac. The right ovary seemed enlarged and adherent. In addition to the principal complaint of dyspareunia and the marked secondary complaint of dysmenorrhea, the patient had daily intermittent lower abdominal pain.

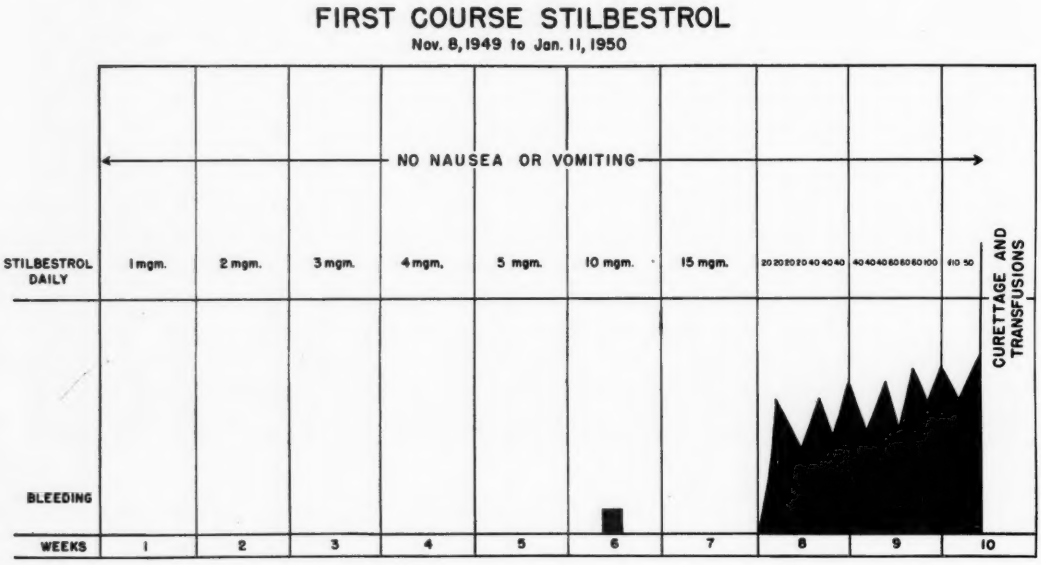

Fig. 5.

Stilbestrol (enteric-coated, Lilly) was given orally, 1 mg. daily the first week, increasing 1 mg. daily each week through 5 mg. daily, then 10, 15, and 20 mg. daily in successive weeks. At this time, because of excessive bleeding, stilbestrol was increased to 60 to 110 mg. daily in one week. After profuse bleeding for ten days, transfusions were given. The uterus seemed enlarged to twice normal size. The right ovary was of normal size and densely adherent laterally. The right uterosacral ligament contained marked induration 2 cm. in diameter, while in the cul-de-sac behind the cervix there was nodular thickening over an area of 3 to 4 cm. The uterine canal measured 9 cm. The cervix was dilated and the uterus thoroughly curetted. A large amount of material was obtained, somewhat yellowish in color and slightly granular in consistency. Microscopic sections (Fig. 2) showed marked endometrial hyperplasia with ''swiss-cheese'' glands, lined with two or three layers of cells with rather frequent mitoses. The stroma was quite cellular.

Following this procedure the same routine of stilbestrol therapy was started again. After five and one-half weeks there was intermittent bleeding until profuse hemorrhage occurred, not improved by increasing the stilbestrol to 60 mg. daily. Seventeen days after the stilbestrol was stopped and after three injections of testosterone propionate, 50 mg., the bleeding ceased. Because of daily lower abdominal pain and continued severe dyspareunia, surgery seemed indicated.

On April 8, 1950, laparotomy revealed marked pelvic endometriosis. The right ovary was small and densely adherent to the undersurface of the broad ligament. The bladder peritoneum appeared to have been advanced on the uterus, although it had not been so treated at the previous operation. Between the bladder wall and anterior surface of the uterus was marked thickening over an area 4 to 5 cm. across and 3 cm. deep. This was separated from the bladder by sharp dissection. This thickened tissue contained multiple small, brownish cavities, typical of endometriosis. There was puckered thickening in the cul-de-sac, but no small surface implants were seen. The entire uterus and cervix and right tube and ovary

were excised. Because of the dyspareunia and the evident residual endometriosis in the cul-de-sac which could not be excised, a presacral sympathectomy was performed. The discoloration in the pelvis and the extensive chocolate material found at the first operation were absent. The nodular thickening between the bladder and the uterus was certainly more extensive than was previously found, and the thickening in the cul-de-sac was very marked. The right ovary was small, slightly cystic, and adherent, and contained puckered endometriosis on the undersurface as seen grossly.

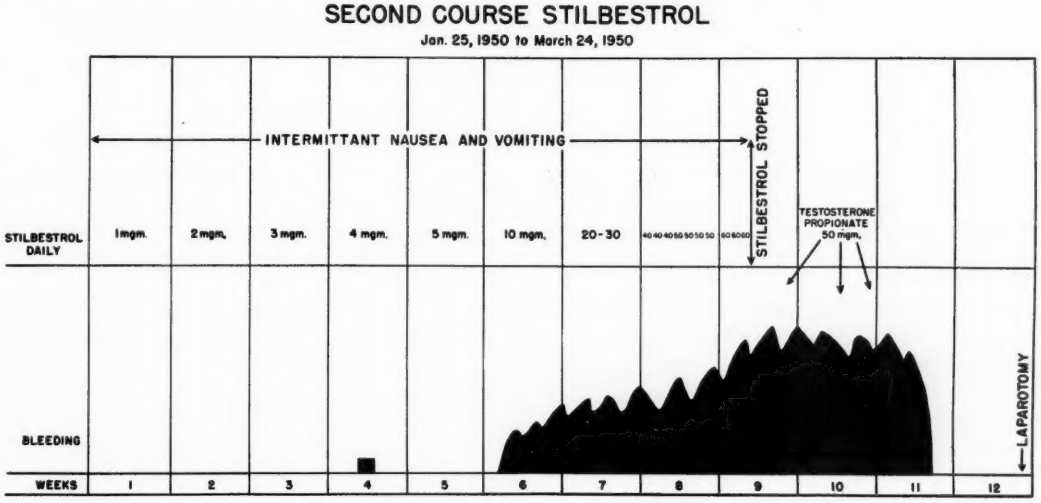

Fig. 6.

Microscopic sections of the endometrium (Fig. 3) showed endometrial hyperplasia with "swiss-cheese" pattern and hyperplastic epithelium. Within the wall of the uterus was moderate adenomyosis with hyperplastic glands and very cellular stroma. Sections of the tissue taken between uterus and bladder (Fig. 4) showed marked endometriosis with cystic glands, hyperplastic epithelium, and cellular stroma. Sections from the right ovary showed a small area of surface endometriosis and a small follicular cyst with active-appearing granulosal cells.

Two and one-half years after the second operation the patient had essentially no abdominal discomfort or dyspareunia. Examination showed relatively little thickening in the cul-de-sac. The atrophic vaginitis, which occurred from castration, was relieved by estrogenic suppositories once or twice weekly. The menopausal symptoms were treated intermittently with phenobarbital.

Summary

A single case of pelvic endometriosis with previous conservative surgery and with recurrence of symptoms and palpable nodules in the cul-de-sac was treated with stilbestrol. The drug was given for four months, but was interrupted at the end of two months and at four months because of profuse vaginal bleeding. The dosage began with 1 mg. daily and was increased to 110 mg. daily with the first half of the treatment. It was increased from 1 mg. to 60 mg. daily with the second half. The symptoms and nodular masses in the cul-de-sac were not improved. Microscopic sections after the second laparotomy showed no atrophic changes in the endometrium or in the endometriosis, but rather the epithelium appeared quite hyperplastic.

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Selected Abstracts

Anesthesia, Analgesia

Browne, O'Donel, McCormick, Victor, and Whyte, F. deBurgh: Trichlorethylene Analgesia in Labour, Brit. M. J. 2: 1556, 1951.

Browne and his associates employed nitrous oxide administered by Minnitt's gas-air machine and Trilene by Steel's inhaler. They found that Minnitt's machine for administering nitrous oxide was too heavy and cumbersome to be of much practical value in the home, while Steel's inhaler for giving Trilene could be easily transported. They state that Trilene is capable of producing pain relief equivalent to that of nitrous oxide. Their experience indicated that Trilene is too high a concentration, or if administered over too long a period of time (2 to 3 hours), lessens uterine tone. They used narcotic drugs in combination with Trilene and reported results with respect to the incidence of forceps, asphyxia, etc., comparable to those obtained with nitrous oxide.

R. GORDON DOUGLAS.

Editorial: Trichlorethylene Analgesia in Labour, Brit. M. J. 1: 443, 1953.

It is pointed out that some form of analgesia is available to every mother in Britain in contrast to certain other countries where little or no effort is made to relieve the pain of childbirth. Reference is made to the extensive investigations that have been carried out with trichlorethylene (Trilene). A committee consisting of obstetricians, anesthetists, midwives, and research workers has not as yet approved an apparatus nor have they consented to the widespread use of Trilene under the direction of midwives. It is pointed out that there is still some justification for caution in the administration of Trilene by virtue of its cumulative effects which demand skill and judgment on the part of the administrator which are not shared by all midwives. It becomes apparent that in spite of the progress that has been made the alleviation of pain in labor remains an urgent and important task for all working in this field.

R. GORDON DOUGLAS.

Rawlings, E. E.: Trichlorethylene in Labour, Brit. M. J. 1: 436, 1953.

The author employed a "Tecota" inhaler (manufactured by Cyprane, Ltd.), an apparatus that contains many safeguards and apparently fulfills most of the specifications enumerated by the Medical Research Council for such apparatus. The paper concerns 400 personal cases, all of which were seen by the author. Three-fourths of the patients were primigravidas and in approximately the same number the analgesia was said to be adequate. There was a slight prolongation of labor if the anesthetic agent was used for a relatively long period of time. There was no significant increase in the operative rate or in the incidence of postpartum hemorrhage. Uterine inertia occasionally developed if the agent

was started too early in labor, but there were no ill effects on the mother or the fetus. The addition of pethidine prior to the administration of Trilene did not increase the incidence of asphyxia.

It was concluded that Trilene produces satisfactory analgesia and that it can be safely combined with pethidine without increasing fetal asphyxia. It can be used by unsupervised midwives who have had some training in its administration. It should not be used until the cervix is 3 fingers dilated and if labor is not completed at the end of 6 hours the administration of Trilene should be stopped. A decrease in the strength and frequency of the uterine contractions is also an indication for discontinuing the analgesic.

R. GORDON DOUGLAS.

Cancer, Malignancies

Rocha, Alberto Henrique: Follow-Up in Cases of Carcinoma of the Cervix of Stage Zero, An. brasil. de ginec. 34: 65, 1952.

The author reports on the type of treatment and subsequent outcome of 28 cases of cancer in situ, Stage 0, discovered from among a group of 3,050 colposcopic examinations made at the Gynecological Clinic of the University of Minas Gerais, Brazil. All 28 clinical cases were confirmed by positive biopsy studies.

Following a visit of Hinselmann in 1949, 4 of the 28 cases were treated by cervical amputation. Before and since that time the surgical methods have been more radical. There were 4 cervical amputations, 2 vaginal hysterectomies, 3 Schauta operations, 1 Wertheim operation, 3 Wertheim operations upon pregnant patients; 12 cases were treated with radium application and 1 was treated with radium and a subsequent Wertheim operation.

The follow-up as correlated to type of initial therapy is tabulated as follows: cervical amputation 4 cases, all without recurrence after 4 years, 2 years, 1 year, and 6 months, respectively; vaginal hysterectomy 2 cases, 1 patient well after 7 years and 1 died postoperatively; one Wertheim operation, the patient alive 2 years later. In the Schauta operation, 3 cases, all were alive and well, 6, 6, and 4 years later, respectively. The three pregnant patients with carcinoma in situ treated by Wertheim operation were alive and well in 2 cases 5 and 2 years later, respectively, while one patient died 2 years following surgery from pulmonary tuberculosis. In the subseries of 12 cases of carcinoma in situ treated by radium applications, dosages not given, one patient was alive and well 6 years later; 1 patient, 5 years later; 1 patient, 4 years later; 4 patients alive and well 3 years later; 3 patients alive and well after 2 years; 1 patient died of postcolostomy cachexia after 1 year; while the last and only patient in the series exhibiting recurrent metastases was a 24-year-old woman treated 4 years earlier with radium therapy (dosage not given).

The author concludes that more radical surgery is indicated in carcinoma in situ, Stage 0, cases of carcinoma of the cervix. He recommends total abdominal or vaginal hysterectomy.

CLAIR E. FOLSOME.

Greene, R. R., Peckham, B. M., Chung, J. T., Bayly, M. A., Benaron, H. B. W., Carrow, Leon A., and Gardner, G. H.: Preinvasive Carcinoma of the Cervix During Pregnancy, Surg., Gynec. & Obst. 96: 7, 1953.

It has quite generally been accepted that pregnancy causes specific changes in the epithelium of the cervix, causing many to believe that the diagnosis of preinvasive carcinoma of the cervix cannot and should not be made in the pregnant patient. The authors do not believe that pregnancy causes specific changes in the cervical epithelium. They do grant that metaplasia and hyperplasia of glandular elements are more common and more prominent during pregnancy than in the nonpregnant state. These changes, however, are not peculiar to pregnancy. They also grant that the surface stratified squamous epithe-

lium of the cervix grows rapidly during pregnancy and a mild increase in the thickness of the basal-cell layer with normal nuclei is occasionally seen. The authors believe that when the criteria are present for the diagnosis of preinvasive carcinoma, such diagnosis should be made regardless of whether the patient is or is not pregnant. The criteria for the diagnosis of preinvasive carcinoma of the cervix are presented in the text and illustrated by numerous reproductions of microscopic sections. Such a diagnosis was made by the authors from biopsies obtained from fourteen pregnant patients. These patients were followed through pregnancy and the puerperium. The lesion persisted after the determination of pregnancy in twelve of the fourteen patients and was found in the biopsies and operative specimens. It is concluded that these lesions are not changes due to pregnancy.

L. M. RANDALL.

Verhagen, A., and Hoffman, K.: Studies on the Diagnosis of Cancer by the Serologic Blood Serum Reaction of Castelli-Gaggini, Zentralbl. f. Gynäk. **74**: 1508, 1952.

Both physicians and laymen are most interested in the early diagnosis of malignant growths. When any new test is proposed for aiding in the early diagnosis of cancer, such a test must be explored and developed in order to determine its specificity and value. In 1950 Castelli and Gaggini reported a reaction of the blood serum to an *Oidium albicans* solution which they thought was specific for malignancy. This test was done as follows: Solutions of blood serum in physiological saline solution in dilutions of 1:10; 1:20; 1:40; 1:80, etc., were set up. To each of these was added 0.5 c.c. of *Oidium albicans broth.* After thorough mixing, the tubes were incubated at 37° C. for 10 hours and then examined for agglutination. When such agglutination appeared in the higher dilutions (minimum 1:160), the test was considered positive for cancer. Control tests using only physiological saline solution should be negative. The *Oidium albicans* solution was made by growing the organism on beer wort agar to which is added 5 per cent of ewes' blood. This growth is buffered with phosphates, killed with formalin, and diluted with saline, so that a minimum of 80 million organisms is present in 1 c.c. of the solution.

The authors have examined the results of this procedure in known cases of carcinoma, especially carcinoma of the female genital tract, in cases of myomas of the uterus, as well as in other proved nonmalignant conditions. In all, 80 such tests were performed. No correlation between proved cases of cancer and positive tests was found. Similarly, many false positives were encountered as well as many false negatives. The authors conclude that the test is not only nonspecific for malignancy but also is of no value in either ruling in or ruling out the presence of malignant tissue in the human organism.

L. B. WINKELSTEIN.

Menstruation

Rauscher, H.: Vaginal Cytological Changes After Progesterone Injection for Secondary Amenorrhea, Wien. klin. Wchnschr. **64**: 301, 1952.

Secondary amenorrhea (with the exclusion of pregnancy) can be due to many different reasons, and may result from general bodily dysfunctions, abnormal hormone production or balance, or functional aberrations of the endometrium. It is necessary therefore to determine, as far as possible, the exact causative factors which produce the amenorrhea before intelligent therapy can be undertaken. When systemic function can be eliminated by physical examination and laboratory procedures the pathological physiology must be contained in the genital tract. Here the two main causes lie between ovarian dysfunction and abnormal endometrial response. The author has found that study of the exfoliated epithelium in the vaginal smear is the most exact and easiest method of determining ovarian function, not only in the secondary but also in the primary amenorrheas, since from such studies the degree of estrogen and progesterone activity can be measured. Furthermore, the effect of injection of these hormones is reflected quickly and easily

by the examination of the vaginal cytology. In a series of patients whose complaint was secondary amenorrhea, progesterone in large doses was given parenterally, and the effect noted. When a good change occurred, the author felt that the basic pathology was essentially ovarian, since the end organ response was positive. However, in many other cases no change in vaginal cytology was noted after injection of large doses of progesterone. This was interpreted as primarily a failure in end organ pathology rather than ovarian dysfunction. The author feels that, progesterone secretion being normal, both the endometrium and the vaginal epithelium fail to respond to its stimulation. This he thought to be due either to a mis-metabolism of the progesterone itself or to blocking of the luteal hormone effect by the end products of hormone metabolites.

L. B. WINKELSTEIN

Miscellaneous

Bookrajian, Edward N., and Truter, William: Stigmonene Bromide in the Diagnosis of Early Pregnancy and the Treatment of Simple Delayed Menstruation, Am. J. M. Sc. **224:** 386, 1952.

Stigmonene Bromide was used by the authors in the treatment of simple delayed menstruation. This cholinergic drug, when administered to normally menstruating women with no pelvic disease or endocrine disturbance, whose periods are delayed, is stated to be a simple and reliable test for pregnancy.

A group of 100 patients, 83 of whom were known to be pregnant, were studied. Each patient was given a daily injection of 1 mg. of Stigmonene Bromide for three successive days. None of the 83 known pregnant women bled following this treatment with the exception of one who had a spontaneous abortion 21 days later. Of the remaining 17 patients, all of whom had a negative biologic test for pregnancy, 16 started to flow 2 to 120 hours following the last injection. The seventeenth case presented a confused clinical and laboratory picture, and it may have been that she was pregnant at the time the injections were given in spite of the negative test. The authors conclude that the use of Stigmonene Bromide is highly accurate as a pregnancy test, is inexpensive, and that it should be used in those cases where menstruation is necessary to put the patient psychologically at ease. No unfavorable reactions to the drug were noted.

HERBERT J. SIMON.

Hay, J. D., and Moss, P. D.: Self Demand Feeding in a Maternity Unit, Brit. M. J. **2:** 1180, 1952.

An experiment in complete self-demand feeding was conducted in a 115 bed maternity unit over a period of 4 months to assess its practicability in such a unit. The program followed was to place the infant at the foot of the mother's bed some 3 to 4 hours after birth, after which time she could feed and cuddle the baby as she desired. The number of feedings was recorded. The method was found to be practicable in that it did not seriously disturb the routine care of the mother. Nipple difficulties and breast engorgement decreased. The nursing staff felt less overworked than with a fixed feeding schedule, but greater vigilance was required at night to reduce the risk of overlaying. Psychologically the mothers felt more possessive and responsible than with fixed schedules.

In a control group followed at home who started on fixed feeding, 34 per cent, of their own initiative, had instituted self-demand. The percentage successfully feeding by self-demand continued higher and over a longer period of time than those begun on a fixed schedule. Weight charts of the infants suggested slightly less loss on discharge in the self-demand group. The aim is to eliminate the difficulties often encountered when the mother finds herself at home for the first time alone with the child. Self-demand anticipates this problem in the hospital. Successful introduction of self-demand requires intensive early postpartum instruction of the mothers and a well-grounded staff. The keynote should be mother-child management with a minimum of interference.

JUSTIN T. CALLAHAN.

Newborn

Bloch, Harry, Scalettar, Howard E., Redner, Bernard, and Hirschl, Daniel: Reduction of Mortality in the Premature Nursery. I. The Declining Role of Infection as a Major Cause of Mortality in the Modern Premature Nursery, J. Pediat. 40: 584, 1952.

While it is generally accepted that the premature infant is highly susceptible to infection, the hazard to life of infection itself in a well-conducted premature nursery would appear to be less important than is generally believed. In order to substantiate the above, the authors (1) evaluated the role of postnatal infection on the mortality of prematures; (2) administered penicillin prophylactically to prematures in order to determine whether this would influence the incidence of infection and the fatality rate.

They emphasized that their investigations were undertaken in a modern premature nursery conducted according to standards established by the American Academy of Pediatrics.

The study was carried out on 180 premature infants. Each was given 150,000 units of procaine penicillin G intramuscularly daily for 5 days, unless the infant failed to survive that long. There were 28 deaths, giving a mortality rate of 15.5 per cent for infants under 2,270 grams at birth; autopsies were done on all of these. Throat cultures were taken from 16 of the infants before and after the penicillin series.

Death due to infection was encountered in only 5 cases and in each of these the diagnosis was bronchopneumonia. In analyzing their findings, the authors conclude that penicillin prophylaxis had no role in maintaining the low incidence of infection. The great loss of premature lives is in the lower weight groups. Since, in the modern premature nursery, infection is no longer of true significance, premature mortality can be reduced by (1) preventing prematurity and, (2) when prematurity does occur, by accelerating the growth processes and development of infants in lower weight groups.

HERBERT J. SIMON.

Robinson, Edward L., and Thompson, Walter L.: Effect on Weight Gain of the Addition of Lactobacillus Acidophilus to the Formula of Newborn Infants, J. Pediat. 41: 395, 1952.

The authors state that it has been common knowledge for many years that breast-fed infants thrive better during the first few months of life than do infants fed cow's milk formulas of the same protein level. The bacterial content of the intestinal tracts and stools of the two groups is quite different. The stool of the breast-fed infant is distinctly acid and gram-positive Lactobacilli predominate. The stools of artificially fed infants are much less acid and coliform-aerogenes predominate. Acidity is thought to promote ready absorption of calcium salts and an acid intestinal flora may be responsible for the synthesis of vitamins and other growth factors.

In view of the above factor, cow's milk formulas were inoculated with cultures of viable *Lactobacillus acidophilus* and fed to a group of infants. A control group of approximately equal number were fed the uninoculated formula. A third group were fed formula inoculated with 2 mg. of folic acid, and a fourth, formula supplemented with folic acid and the Lactobacilli.

After a study of the results the authors felt that infants fed on formulas supplemented with *L. acidophilus* showed significantly larger weight gains than did the controls. The addition of folic acid had no significant effect on the weight gain. The addition of *L. acidophilus* to the formula of partially breast-fed babies had no effect on the weight gain.

Colostrum may contain a factor which stimulates increased weight gain during the first month of life. By supplementing the formula of the completely bottle-fed infant with *L. acidophilus* for the first few days of life, this increase in weight gain may be approximately equaled.

HERBERT J. SIMON.

Quick, Armand J., Murat, Luiz G., Hussey, Clara V., and Burgess, Gordon F.: The Prothrombin in the Newborn, Surg., Gynec. & Obst. **95**: 109, 1952.

The free and total prothrombin and the labile factor were quantitatively determined in the maternal, the cord, and the infant's blood when vitamin K was administered ante partum and when it was omitted. A method is detailed for a one-stage test for prothrombin which measures only the free or active prothrombin and is not influenced by the inactive prothrombin (prothrombinogen).

Two methods for determination of total prothrombin time are discussed. The results of the two methods agree well. A method for determination of the labile factor is also discussed. A table gives the results of the four tests when no vitamin K has been administered and in cases when it was given.

When the mother receives a water-soluble vitamin K compound prior to delivery the prothrombin time of the maternal, cord, and infant's blood is normal, 12 seconds. If no vitamin K is given the cord blood almost invariably shows a moderately prolonged prothrombin time. Most unexpected was the finding that the prothrombin time and total prothrombin time are essentially the same in the cord and in the infant's blood. In the newborn the total prothrombin time is equal only to the free prothrombin time. The labile factor was found to be roughly the same in both the mother's and in the baby's blood, and vitamin K appears to have no influence on its concentration. When the available vitamin K is adequate, the fetus can apparently produce prothrombin readily and maintain a prothrombin time equal to that of the adult. When the mother is not given vitamin K the fetus generally does not secure sufficient quantity of the vitamin to have a prothrombin time of 12 seconds. It is highly probable that it is primarily the active prothrombin on which hemostasis depends. Consequently, when an infant has a prothrombin time of 12 seconds the hemostasis appears to be as normal as that of the adult even though the total prothrombin is only 25 per cent. The infant, nevertheless, is presumably in a somewhat precarious situation. He probably has little or no store of vitamin K and none is probably immediately available from the digestive tract. The metabolic demands deplete the free prothrombin rapidly and, if one postulates that the prothrombinogen functions as a reserve, the lost prothrombin cannot be promptly replaced because of the absence of the latter. The total prothrombin, which in the normal human adult consists of free and inactive prothrombin (prothrombinogen), was found quantitatively unchanged in the parturient mother.

L. M. RANDALL.

Sulamaa, Matti, and Vara, Paavo: An Investigation Into the Occurrence of Perinatal Subdural Hematoma; Its Diagnosis and Treatment, Acta obst. et gynec. Scandinav. **31**: 400, 1952.

The authors report experience with subdural hematoma in the newborn as recorded in the autopsy files of the women's and children's clinics of the University of Helsinki during the period 1925 to 1950. The incidence of subdural hematoma after full-term delivery was 0.31 per cent, and this figure would be appreciably increased if premature deliveries were included. The principal etiological factors observed were prematurity, late pregnancy toxemia, cephalopelvic disproportion, and operative deliveries of various types. The possibility of subdural hematoma is often overlooked in premature infants, or in newborn babies exhibiting icterus and labored respiration. This is particularly true since signs such as drowsiness, lack of muscle tone, and general hypoactivity are in no way pathognomonic. The authors believe the most reliable diagnostic procedure to be early lumbar puncture performed with correct technique. In the autopsy records of the Children's Clinic, 34 per cent of the babies with final pathological diagnosis of perinatal subdural hematoma died without this procedure having been performed; appropriate surgical treatment might have been lifesaving in at least some of these cases. Gradual evacuation of the hematoma contents by means of repeated small punctures begun early was the treatment followed in cases in this series diagnosed in time. No long-term follow-up on any of the 11 surviving patients was available at the time of submission of the present article.

DOUGLAS M. HAYNES.

Pregnancy, Complications

Chaudhuri, S.: Vitamin B_{12} in Megaloblastic Anemia of Pregnancy and Tropical Nutritional Macrocytic Anemia, Brit. M. J. 2: 825, 1951.

This report describes the hematological responses of 16 patients admitted to the hospital with mebaloblastic anemia of pregnancy and 5 patients with tropical megaloblastic anemia treated with vitamin B_{12}. Five of the patients were pregnant (last trimester of pregnancy). Eleven were parturient less than three months, 9 within 15 days of delivery. Treatment was instituted after the first blood examination. Vitamin B_{12} was administered intramuscularly in 20 μg doses either every other day or every fifth day depending on the status of the patient. Daily dosages ranged from 4 to 11 μg. Patients were treated from 12 to 54 days. The vitamin was discontinued when the blood findings became stationary. Reticulocytosis occurred in all cases after treatment and varied from 3.5 to 25 per cent. Mean hemoglobin, red blood cell count, and cell volume of these patients before treatment were 4.0 Gm. per 100 ml., 1.35 million per cubic millimeter, and 13.1 per cent; after treatment they were 9.8 Gm., 3.6 million, and 28.7 per cent, respectively. The total proteins before treatment were low in all cases, with a low albumin and high globulin in many cases. In these there was generally an inverted A/G ratio. One patient with the minimum reticulocyte response was subsequently treated with parenteral folic acid to which she responded rapidly. Dosage of vitamin B_{12} required for response is estimated as ranging from 4 to 10 μg per day, depending on the severity of the case. Higher doses are required during pregnancy. From this and other evidence the conclusion is reached that "vitamin B_{12} is effective in most cases of tropical megaloblastic anemia and megaloblastic anemia of pregnancy and the puerperium, but that the dosage is higher than that needed in Addisonian pernicious anemia."

ROY W. BONSNES.

Campbell, W. A. B.: Influenza in Early Pregnancy. Effects on the Foetus, Lancet 1: 173, 1953.

A fairly severe epidemic of influenza (A-prime) occurred in Northern Ireland in December and January, 1950-1951. A survey was subsequently made to include mothers attending the antenatal clinics of the Belfast City Hospital, the Royal Maternity Hospital, and the maternity and child-welfare service of Belfast Corporation. Nine hundred eighty-nine births were studied; 164 occurred in mothers who had had influenza during the first 4 months of pregnancy. The others served as controls. All malformations were carefully studied and it was concluded that influenza in the early months of pregnancy did not add to the risk of stillbirth or fetal abnormality.

R. GORDON DOUGLAS.

Benson, Ralph C., and Chappell, Clifford C.: Vulvar Fluorescence in Normal and Abnormal Pregnancy, Surg., Gynec. & Obst. 95: 102, 1952.

The authors relate their experience with fluorescence studies among 200 women in whom there was clinical evidence of pregnancy, possible pregnancy, or recent pregnancy. Whenever possible, serial observations were recorded. The basic intrinsic and extrinsic colors of vulvar fluorescence, and their changing pattern, can be demonstrated successfully in near darkness with any of several portable ultraviolet lamps now available, fitted with either a Corning 5874 or Kopp 41 filter, employing either a General Electric or Westinghouse No. CH4 mercury vapor lamp. Elimination of other light and dark adaptation is required of the observer. The characteristic color changes for pregnancy and the puerperium are described. In cases of abortion the color change characteristic of pregnancy is lost after the fourth or fifth day following interruption. It is suggested that vulvar fluorescence may be used as a guide for therapy when abortion is threatened. The authors indicate the desirability of further study of vulvar fluorescence.

L. M. RANDALL.

Klopper, Arnold, and Ventura, S.: Iron Metabolism in Pregnancy, Brit. M. J. 2: 1251, 1951.

In 1,804 patients delivered by the obstetric service of the Hammersmith Hospital, 54 patients with hemoglobin below 10 Gm. per cent were observed. Eight, on re-examination, had borderline hemoglobin values and responded to oral iron. Two had mild cases of familial acholuric jaundice and another a congenital hemolytic anemia of obscure origin. Five had cases of normocytic anemia with no complaints or symptoms, nor any signs of disease on examination. Their serum iron determinations were normal, but they had generally low iron-binding capacity, serum copper, and free erythrocyte protoporphyrin. They were considered to have sufficient iron available for hemopoiesis, but had a possible defect in iron utilization; thus, little or no benefit was to be expected from the administration of iron. The remaining 38 had classical cases of microcytic hypochromic anemia. Detailed studies of 9 of these showed their serum iron to be low, the iron-binding capacity to be increased, the serum copper high, and the free erythrocyte protoporphyrin increased. These values were then measured in 8 of the patients who received as treatment iron as Ferrivenin administered intravenously weekly in 100 mg. doses until the hemoglobin reached 10.2 Gm. Five hundred to 2,000 mg. of iron were required. The response was as might be expected with the general trend toward normal pregnant values, except in the case of protoporphyrin, which showed no general pattern in its response to iron. The patients all improved clinically. The effectiveness of intravenous Ferrivenin was further evaluated in 27 more patients with hypochromic anemia of pregnancy. From these data they calculate that during the last quarter of pregnancy for each 100 mg. of iron injected a rise of only 0.436 Gm. of hemoglobin can be expected (compared with 0.65 Gm. in the nonpregnant state) since about one-third of the iron injected is lost to the fetus.

ROY W. BONSNES.

Magee, H. E., and Milligan, E. H.: Haemoglobin Levels Before and After Labour, Brit. M. J. 2: 1307, 1951.

The results of a survey of the hemoglobin values observed in 2,087 women during pregnancy and for a year or more following delivery in the area of Manchester, England, are reported in this paper. Hemoglobin was determined as alkaline hematin using a M. R. C. gray-wedge photometer. The average results during the antenatal period can be described by a curve which declines from 93 per cent (Haldane) at the eighth week to a minimum of about 81 per cent between the thirty-second and thirty-fourth weeks, then rises again to nearly 85 per cent at the thirty-ninth week. The average results observed during the postnatal period can be described by a straight line increasing from 85 per cent at the fourth to 90.5 per cent at the sixty-fifth postnatal week. These results tended to be more variable than those during the antenatal period. Those taking iron had higher levels throughout. The effects of iron medication were better the longer the iron was taken. With increasing parity there was a decrease in the mean concentration of hemoglobin, both ante partum and post partum. Low hemoglobin and clinically graded undernutrition did not necessarily parallel each other, though the incidence of clinically graded undernutrition increased with increasing parity, particularly during the antenatal period. No relationship was observed between hemoglobin levels and systolic blood pressure.

ROY W. BONSNES.

Benstead, N., and Theobald, G. W.: Iron and the "Physiological" Anemia of Pregnancy, Brit. M. J. 1: 407, 1952.

The range of initial hemoglobin values of 2,000 consecutive antenatal patients, pregnant for less than 17 weeks, who registered at the antenatal clinic of St. Luke's Maternity Hospital, Bradford, England, between January and October, 1950, are reported. Sixty per cent had values less than 12 Gm. per cent; 6.5 per cent less than 10 Gm. per cent. To test the effectiveness of iron administration during pregnancy in this population, small groups of these patients in the third decade and reasonably well matched as

to other variables were selected. All received tablets containing calcium and vitamins and the extra rations and vitamins supplied by the Ministry of Food. All had initial hemoglobin levels of 11 Gm. per cent or better. Seventy-two such patients were divided into two matched groups, A and B. Those in Group A received 2 tablets containing 195 mg. ferrous sulfate, 2.4 mg. copper sulfate, and 2.4 mg. manganous sulfate, three times a day throughout pregnancy. Those in Group B received placebos. The average hemoglobin and the mean corpuscular hemoglobin values of Group A remained fairly constant and normal for nonpregnant individuals throughout pregnancy and were significantly higher than those observed in the control Group B from the twenty-fourth week on through the puerperium. The average packed cell volume was significantly higher than that observed in the control group from the twenty-eighth week to term. Administration of iron, either as the ferrous sulfate tablets as above or as Mol-Iron tablets (each tablet containing 195 mg. ferrous sulfate and 3 mg. molybdenum oxide), 2 tablets three times a day for 8 weeks starting at the twenty-fourth week, to two smaller groups of patients similar to those described above resulted in a marked improvement in the blood picture as compared with that of the control group by the twenty-eighth week, and in essentially normal nonpregnant values by the thirty-second week. These values were maintained throughout the rest of pregnancy. No difference was observed in the effectiveness of Mol-Iron as compared to that of ferrous sulfate when physiological response was evaluated. However, Mol-Iron tablets were better tolerated. The authors conclude that the so-called physiological anemia of pregnancy is actually an indication of iron deficiency and that with an adequate intake of iron, normal nonpregnant blood values for hemoglobin may be maintained through pregnancy.

ROY W. BONSNES.

Puerperium

Arthur, Hugh R., and Chalmers, J. D.: Post-partum Blood Pressure Levels, Edinburgh M. J. 59: 555, 1952.

An examination was made of the records of 2,001 obstetric patients to determine whether labor had any uniform effect on blood pressure and whether there are any cases in which unexpected hypertension does occur. A blood pressure of 140/90 mm. Hg was accepted as the upper limit of normal. Excluding patients with known antenatal hypertension and some whose antenatal records were incomplete, 5.3 per cent of the total 2,001 patients showed an unexpected immediate postpartum hypertension. In the majority (81 of 106) this hypertension was mild. The follow-up is incomplete and thus not interpretable but 58 of 86 had normal blood pressures on discharge and 79 of 82 were normal "at the post-natal clinic." "It is thus apparent that in only a small percentage of patients is the unexpected immediate post-partum hypertension an indication of a truly hypertensive state." On further analysis, no common factor was found to explain the etiology of the postpartum rise in blood pressure.

JOHN L. MCKELVEY.

McLaren, Hugh C.: The Involution of the Cervix, Brit. M. J. 1: 347, 1952.

Dr. McLaren, after studying 121 postnatal cervices which showed erosions, drew the following conclusions:

1. Postnatal erosions are physiological.
2. They do not cause backache.
3. They are rarely the source of vaginal discharge.

The spontaneous healing rate in his series was 64 per cent during the first twenty weeks after delivery. He proposes that rather than routine postpartum cauterization a few weeks after delivery, a cauterization be used only in the 5 or 10 per cent of cervical erosions which are producing leukorrhea more than twenty weeks after delivery.

WILLIAM F. FINN.

Radiation

Nyiri, Stefan: Prothrombin Values Before and After X-ray Therapy, Zentralbl. f. Gynäk. **74:** 2013, 1952.

The level of the prothrombin in the blood in patients with genital carcinoma was examined before and after radiation therapy. This was done in order to see whether this could be used as an index of clinical value in the treatment and management of the disorder. All stages of genital carcinoma from Stage I to Stage IV were used for study. Studies of prothrombin values were made before x-ray therapy was given; after a first series of treatments, and for variable periods of time after a second series of treatments had been completed. Forty-eight cases of carcinoma of all types were studied. It was found, in general, that an increase in the prothrombin values occurred. This increase, in a previous hypoprothrombinemia, paralleled not only the effects of radiation on the body, but also served as an adequate indication for the amount of therapy as well as a prognostic sign for the effect of treatment. L. B. WINKELSTEIN.

Item

Italian Society for Obstetrics and Gynecology

The Forty-third Meeting of the Italian Society for Obstetrics and Gynecology will be held in Rome, in Palazzo Barberini, between Sept. 21 and Sept. 24, 1953.

The main subjects on the agenda are:

Prof. Luigi Cattaneo: Modern Trends in Gynecological Surgery.

Prof. Mario Masazza: Allergic Phenomena in Obstetrics and Gynecology.

Participation in the Congress is free of charge to all members of Italian or foreign societies of obstetrics and gynecology. Otherwise the fee is 5,000 lire.

For further information write to: Professor Piero Cattaneo, Secretary-general, Clinica Ostetrica e Ginecologica dell'Università di Roma, Casella Postale Roma Nomentano 7171. All payments should be addressed to the Treasurer: Dottor Luigi Carenza, Conto Corrente Postale 1/561, Roma Nomentano 7171. The registration fee can also be paid on arrival in Rome.

In Memoriam

Thomas Stephen Cullen

WITH the death of Thomas Stephen Cullen on March 4, 1953, there passed from our midst the last of the great figures in medicine who came as interns to the Johns Hopkins in its infancy. He came as an intern in Pathology under Dr. Welch in 1891 and retired as Professor of Gynecology in 1939.

Dr. Cullen was born in the bush country of Ontario, north of Belleville, in a town which died with the death of the logging industry of that part of Ontario. He was of English-North Irish descent, the first son of a Methodist minister of a country parish. His early education was interrupted by the moving of his father from parish to parish. Finally, during his later adolescent years his father, the Rev. Stephen Cullen, was given a parish in Toronto. Thus, young Tom attended the Dufferin School and later Jarvis Collegiate Institute. Judged by today's softer standards his boyhood would be considered rugged and poor. Rugged it was, but in referring to it in later life Dr. Cullen considered it anything but poor. To him was offered the privilege of fishing, hunting, and tramping in the woods, more than which no red-blooded boy could ask. His love for the bush country remained with him throughout life and, although he visited Europe several times for professional reasons, his vacations were all spent in the Ontario Lake District north of Toronto.

At the age of 14 he attained financial independence by starting a paper route. It was required that he be at the Toronto Mail office at 4:00 A.M. every weekday morning. The habit of early rising remained with him throughout life, a fact all too well known by his residents whom he delighted in calling up at 6:00 or 6:30 in the morning.

In the fall of 1886, two months before his eighteenth birthday, Tom Cullen entered Toronto University Medical School. This undertaking he financed himself by doing odd jobs as well as by his regular income from his paper route.

It was while interning at the old Toronto General Hospital that Tom Cullen first heard of Hopkins through his friend, Lewellys Barker, who had secured an internship under Osler. Cullen tried to obtain a similar position, but Osler's staff was full. In the spring of 1891, Howard Kelly arranged a canoe trip down the Magnetawan River through Dr. Leslie Sweetman of Toronto. Dr. Sweetman, who was Cullen's preceptor, took the opportunity of arranging an operative clinic for Kelly in Toronto on the day preceding

the canoe trip. Cullen and Barker were assigned to the surgical team. Cullen had never before seen such surgical dexterity and decided then and there to attempt to get on Dr. Kelly's staff. Before Kelly left Toronto Dr. Cullen had been promised a gynecological internship at Hopkins. There was a lapse of six months between the end of his Toronto appointment and the beginning of this internship. Dr. Kelly arranged for him to spend this time with Dr. Welch in Pathology. This short service with Welch gave him a feeling for pathology which he never lost and which in my opinion was responsible for Dr. Cullen's greatest contribution to gynecology, namely the establishment of a laboratory in Gynecological Pathology which became the mother of many of the gynecological pathology laboratories in this country.

After finishing his residency training under his chief and idol, Howard Kelly, Cullen went into practice in Baltimore. Immediately he began working and publishing. His first book, *Cancer of the Uterus,* appeared in 1900. In 1908 his monograph on *Adenomyomata of the Uterus* was published. The next year *Myomata of the Uterus* came out with Dr. Kelly as co-author. In 1916 *The Embryology, Anatomy and Diseases of the Umbilicus* made its appearance and, finally, a small volume in 1920 on *Henry Mills Hurd, The First Superintendent of The Johns Hopkins Hospital.* In judging these works from the perspective of many years, I believe it is fair to rank at least two as classics—*Cancer of the Uterus* and *Adenomyomata of the Uterus.* In addition, he was the author of more than one hundred papers on gynecology, but particularly on the pathology of the female reproductive tract.

He was made Professor of Clinical Gynecology with the hospital appointment of Visiting Gynecologist in Charge in 1919 and in 1932 he became Professor of Gynecology, a position which he held until his retirement in 1939 at the age of 70. He taught every class that graduated from the Hopkins Medical School up to his retirement and after his retirement from active teaching he returned on invitation to hold one clinic for each group of students until his seventy-ninth year. Those of us who remember "T. S." in the operating room recall a rotund individual with a prominent ruddy nose and tremendous eyebrows projecting over his surgical mask, but even the bushy eyebrows failed to conceal his sharp flashy eyes. He was anything but a quiet individual and not averse to a little horseplay at times. He loved to "ride" his house staff about their mistaken diagnoses, but all in good nature. Promptness was one of Dr. Cullen's greatest virtues, if it can be considered a virtue by the operating-room staff to arrive at 7:30 in the morning for an operation posted for 8:00. Perhaps his greatest single characteristic was his boundless energy which persisted well into his latter years.

One of Dr. Cullen's greatest contributions to Hopkins and to the medical world was his part in the establishment of a school of art as applied to medicine. In 1894 a curly-headed artistic boy came to Baltimore from Germany. Max Brödel was maintained at Dr. Kelly's expense and was privately instructing some young artists. The Mayo Clinic was quick to recognize his skill and made him a handsome offer which gave him financial

security. Single handed, Dr. Cullen persuaded Henry Walters to guarantee $5,000.00 a year for Mr. Brödel's salary for three years. At the end of that time Mr. Walters gave the University $110,000 for the permanent endowment of the Art Department. Thus, it was made possible for Max Brödel to make his influence felt as a teacher of medical art rather than simply as a superb illustrator, which would have been his lot if he had gone to Rochester.

Dr. Cullen's influence was not confined to gynecology or to the environment of Hopkins. He was the first to wage a war for the education of the public regarding cancer and his first article for lay consumption appeared in *The Ladies' Home Journal* in 1913. Because of this article he was made the target of many medical bigwigs of the time, but this only made him more determined.

In 1930 he succeeded Dr. Welch on the Maryland State Board of Health, a position which he held until his death. While on this board he waged an active campaign against pollution of the waters of the Chesapeake Bay.

He was a member of the Board of the Enoch Pratt Library for many years and gave it devoted service. He was elected to the Presidency of that Board in 1938 and re-elected every year to his death.

After he suffered a partial paralysis from a stroke about two years before his death, his indomitable spirit lived on. He was determined to make one more trip to Canada and see the Magnetawan River and his beloved Lake Ahmic. This he accomplished last summer by means of a private railroad car and he re-lived on the shores of the lake the many happy summers which he had spent with Kelly, Brödel, and Flexner.

On February 26 there was held the first reunion of Hopkins residents in Gynecology. Dr. Cullen enjoyed himself thoroughly and it was a treat for the younger men to visit with him. The next night he attended the biennial dinner of the Hopkins Medical and Surgical Society. He left before the speaking began and many of his old students shook his hand as he departed. He came home in good spirits, smoked a cigar, and spoke to Mrs. Cullen of the good time that he had had at the two dinners. Early the next morning he had another stroke which proved to be fatal four days later. Although a feeling of sadness is inevitable with the passing of a great character, one cannot help but believe that it would have been planned exactly that way had he been master of his own destiny.

Richard W. Te Linde

Irving L. Frank

Dr. Irving L. Frank of Philadelphia, a valued contributor to the Abstract Department of the JOURNAL, passed away on June 3, 1953. The Editors desire to express their regrets for his untimely death.